Medical Journal of the
Islamic Republic of Iran

Volume 17
Number 4
Winter 1382
February 2004

IMPACT OF IODIZED OIL INJECTION DURING PREGNANCY ON THYROID FUNCTION TESTS OF OFFSPRINGS

NAVID SAADAT, ROBABEH SHEIKHOLESLAM, AND FEREIDOUN AZIZI

From the Endocrine Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, I.R. Iran.

ABSTRACT

Previous studies have shown that injection of iodized oil in pregnant women can be used as a prophylactic strategy for iodine deficiency disorders and may improve the growth indices of their offspring. Since administration of pharmacological doses of iodine may lead occasionally to large goiter and rarely to hypothyroidism, in the present study the thyroid function tests of neonates and infants born to women who had received 480 mg iodized oil intramuscularly during pregnancy were assessed and compared to those of a control group.

Of 277 cord blood samples obtained from Mazandaran and Khohkiluyeh-Boyerahmad provinces, 125 made up the case (injected) and 152 the control (non-injected) group. Of 1026 blood samples of the neonates and infants from Mazandaran province, 544 made up the case and 482 the control group. Serum T_4, T_3 and TSH concentrations were measured with RIA kits.

In the cord blood samples, mean serum T_4 in cases who had received iodized oil was lower than that of the control group: 140±32 vs. 149±33 nmol/L, respectively; $p<0.03$. T_3 and TSH were not however different. In the neonates and infants, T_4 and T_3 concentrations were significantly higher in the case than control group: 178±40 vs. 168±39 and 3.5±0.02 vs. 3.0±0.02 nmol/L, respectively, both $p<0.001$. In contrast, TSH concentrations were lower in the experimental group in comparison to control: 2.6±2.2 vs. 3.1±2.9 mU/L, respectively; $p<0.001$. Increased T_3 and decreased TSH were seen in infants of mothers who were injected in the second and third trimesters of pregnancy.

Injection of iodized oil in pregnant women does not cause hypothyroidism in the offspings, however it does cause a transient increase in serum thyroid hormones and a decrease in TSH concentrations.

MJIRI, Vol. 17, No. 4, 277-283, 2004.

Keywords: Iodized oil, Pregnancy, Neonates, Thyroid function

INTRODUCTION

For over thirty years, iodized oil has been successfully used for the prevention and treatment of iodine deficiency disorders (IDD).[1] Although iodized salt consumption has been successfully employed in the pro-

Address for correspondence and reprint requests: Professor F. Azizi, P.O. Box 19395-4763, Tehran, I.R. Iran. Tel: 98 21 2409309, Fax: 98 21 2402463, E-mail: azizi@erc-iran.com.

phylaxis of IDD,[2] iodized oil administration is recommended in severely deficient regions with mental and growth retardation or hypothyroidism.[3-7] Prophylaxis of endemic cretinism[8,9] and neonatal hypothyroidism will only be achieved when iodized oil is administered before conception and during pregnancy.[10,11]

Not only does iodized oil prevent endemic cretinism[12-14] and mental retardation[15-17] but it also decreases fetal and perinatal mortality[18-20] and increases birth weight[21-23] Previous studies demonstrated that iodized oil administration to women before, or at any time during gestation was safe[24] and devoid of adverse effects for the pregnant mother.[25] However, it is well known that the fetal thyroid may be unable to avoid the Wolff-Chaikoff phenomenon.[26-28] It has been demonstrated that exposure to high doses of iodine in pregnant women may cause goiter and hypothyroidism in their newborn.[30-32]

Goiter, physical and intellectual growth retardation have been prevalent in the Islamic Republic of Iran[33-35] and attempts to control IDD have been made by universal salt iodization.[36] In the national program for control of IDD in Iran, iodized oil was administered to people residing in the hyperendemic regions.[4] Two provinces of Mazandaran and Kohkiluyeh-Boyerahmadi were covered in this national program. This study was conducted in 1993-94 in order to assess the effect of iodized oil injection in pregnant women on the thyroid function of their offsprings in these two provinces.

SUBJECTS AND METHODS

A 1989 national survey of goiter in the Islamic Republic of Iran showed that goiter prevailed in schoolchildren in most provinces at a rate of between 30-80%[7] and it was estimated that some 20 million people were at risk of iodine deficiency. Iran's National Committee for Control of IDD (NCC-IDD) was established in 1989. The production and distribution of iodized salt, with 40 mg of potassium iodide per kg of sodium chloride and the education of policymakers, health personnel and public was begun in 1990. However, a rapid survey of iodized salt consumption in 1993 showed that less than 40% of the households in rural areas consumed iodized salt with a mean urinary iodine from 5.0 to 8.2mg/dL in spot locations. Therefore, NCC-IDD decided to use iodized oil prophylaxis for areas with goiter prevalence of over 30% in schoolchildren.

Schoolchildren of Mazandaran and Kohkiluyeh & Boyerahmad provinces had severe iodine deficiency with total goiter rate of 90 and 67% respectively in the previous national survey in 1989.[33] Urinary iodine excretions in the 2 locations were 33.6±36.1 (median 31.2) and 24.0±16.6 mg/L (median 23.2).[37] Therefore, all inhabitants of the rural regions in both provinces were included in the national program of iodized oil supplementation.

Six hundred sixty nine healthy pregnant women from endemic rural regions of Mazandaran and Kohkiluyeh-Boyerahmad received one milliliter containing 480 mg iodized oil (Lipidol, Laboratory Guerbet, France) intramuscularly. Controls were randomly selected among non-injected (at the time of this study) pregnant women's infants. We studied 277 cord blood samples, 125 in the case (injected) and 152 in the control (non-injected) groups. We also took 1026 blood samples from the neonates and infants, for up to 12 months of age, 544 in the case and 482 in the control groups. Complete data in 62, 79 and 170 infants whose mothers received iodized oil injection during the first, second and third trimesters, respectively, were available. The date of iodized oil injection during pregnancy and the age of the neonate were recorded. In all subjects, whole blood was obtained, centrifuged and serum freezed immediately and transported to the central laboratory of the Endocrine Research Center.

Serum T_4, T_3 and TSH concentrations were measured with commercial radioimmunoassay (RIA) kits (Amersham, UK). The intra-assay and interassay coefficient of variations were both below 10%. This study was approved by the Ethics Committee of the Endocrine Research Center.

Results were expressed as mean±SD. Student's t-test and ANOVA were used to compare the means between groups. Statistical significance was determined at the $p<0.05$ level of confidence.

RESULTS

Cord blood

Serum T_4 concentration was marginally but significantly lower in the experimental group when compared to the control: 140±32 vs. 149±33 nmol/L, respectively, $p<0.03$. There was no statistical difference in T_3 and TSH concentrations between the experimental and control groups: 0.86±0.48 vs. 0.92±0.48 nmol/L and 6.7±5.5 vs. 6.9±5.3 mU/L, respectively. Serum TSH concentration in cord blood samples was more than 20 mU/L in 5 and 6 of iodized oil injected and control mothers, respectively. Serum T_4, T_3 and TSH concentrations of cord blood samples in those who had TSH over 20 mU/L are shown in Table I. There is no statistical difference in T_4, T_3 and TSH concentrations between the two groups.

Neonates

Mean serum T_4 and T_3 concentrations were significantly higher in the experimental group as compared to the controls: T_4; 178±40 vs. 168±39, $p<0.001$ and T_3; 3.5±0.02 vs. 3.0±0.02 nmol/L respectively, $p<0.001$. Mean serum TSH concentration was lower in the children of

injected subjects as compared to the control group: 2.6±2.2 vs. 3.1±2.9 mU/L, respectively, $p<0.001$. Serum concentrations of T_4, T_3 and TSH were compared in various groups of infants aged <1,2,3,4,5 and >6 months of age. Table II shows serum T_4, T_3 and TSH concentrations in neonates and infants whose mothers received iodized oil in the first, second and third trimesters of pregnancy and controls. There is no significant difference in T_4, T_3 and TSH concentrations between infants whose mothers were injected with iodized oil in the first trimester of pregnancy, and infants of the control group. Serum T_3 showed an increase and serum TSH a decrease in infants whose mothers were treated with iodized oil in the second and third trimesters of pregnancy when compared to control infants. Serum T_4 was also increased in these infants, but it was statistically significant only in infants of mothers injected in their third trimester.

In infants whose mothers received iodized oil during the second trimester of pregnancy, serum T_3 was higher and serum TSH was lower than in controls in infants less than one month of age: 3.9±0.3 vs. 2.5±0.2 nmol/L ($p<0.001$) and 2.7±0.36 vs. 4.4±0.29 mU/L ($p<0.02$), respectively. Serum TSH was also significantly decreased in the second months of life, as compared to infants of the control group: 1.8±0.28 vs. 2.9±0.25 mU/L, $p<0.013$. Serum T_4 in infants <1 to 6 months old and serum T_3 in 2 to 6 months old and serum TSH levels in 3 to 6 months old infants of this group were not significantly different from controls.

Fig. 1 shows serum T_4, T_3 and TSH concentrations in infants whose mothers received iodized oil during the last trimester of pregnancy. Serum T_4 was significantly increased in the below one and 2 month old infants; serum T_3 was increased in the second one, 3, 4, and 5 months old infants; serum TSH was decreased in 2 and 3 months old infants, as compared to control infants. Serum T_4, T_3 and TSH concentrations in infants whose

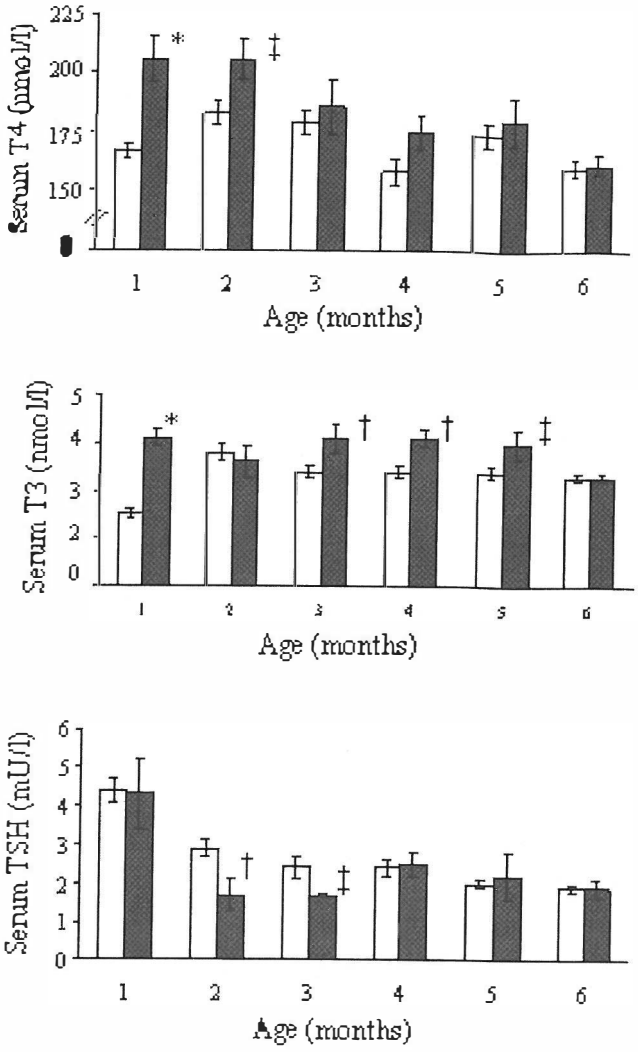

Fig. 1. Serum T_4, T_3 and TSH concentrations in neonates and infants whose mothers received 480 mg iodized oil in the third trimester of pregnancy (case) ■ and control neonates and infants □. *$p<0.001$, †$p<0.02$, ‡$p<0.04$, compared to control group.

Table I. Serum T_4, T_3 and TSH concentrations of cord blood samples of case and control mothers who had TSH of more than 20 mU/L.

Groups		T_4 (nmol/L)	T_3 (nmol/L)	TSH (mU/L)
Case				
	1	91	0.61	41
	2	151	1.08	23
	3	167	1.08	21
	4	145	1.02	25
	5	192	0.53	23
Control				
	6	115	0.77	33
	7	116	1.38	22
	8	129	1.67	23
	9	117	0.61	39
	10	206	2.61	21
	11	133	0.62	24

prevention and control of iodine deficiency disorders. Amsterdam: Elsevier, pp. 127-134, 1987.
7. Lu TZ, Ma T: A clinical investigation in China on the use of oral vs. intramuscular iodized oil in the treatment of endemic goiter. In: Medeiros-Neto G, Maciel RMB, Halpern A, (eds.), Iodine deficiency disorders and congenital hypothyroidism. Sao Paulo, Brasil, pp. 103-9, 1986.
8. Pretell EA: The optimal program for prophylaxis of endemic goiter with iodized oil. In: Stanbury JB, Kroc R, (eds.), Human development and the thyroid gland. New York: Plenum, pp. 267-288, 1972.
9. Thilly CH, Bourdoux P, Vanderpas J, Mafuta M, Berquist H, Due D, Delange F, Ermans AM: Epidemiology and prophylaxis of endemic goiter in developing countries. New York: Raven Press, Serono Symposia 22: 45-59, 1985.
10. Buttfield IH, Pharoah POD, Hetzel BS: Evidence of prevention of neurological defects in New Guinea children by iodized oil injection of mothers prior to pregnancy. In: Fellinger K, Hofer R, (eds.), Further advances in thyroid research. Vienna: Wiener Medizinsche Akademie, pp. 53-59, 1971.
11. Malamos B, Koutras DA, Mantzos J, et al: Endemic goiter in Greece: effects of iodized oil injection. Metabolism 19: 569-580, 1970.
12. Benmiloud M, Chaouki ML, Gutekunst R, Teichert HM, Wood WG, Dunn JT: Oral iodized oil for correcting iodine deficiency: optimal dosing and outcome indicator selection. J Clin Endocrinol Metab 79: 20-24, 1994.
13. Chaouki ML, Benmiloud M: Prevention of iodine deficiency disorders by oral administration of iodized oil during pregnancy. Eur J Endocrinol 130: 547-551, 1994.
14. Delange F: Administration of iodized oil during pregnancy: a summary of the published evidence. Bull World Heath Organ 74: 101-108, 1996.
15. Eltom M, Karlsson FA, Kamal AM, Bostrom H, Dahlberg PA: The effectiveness of oral iodized oil in the treatment and prophylaxis of endemic goiter. J Clin Endocrinol Metab 61: 1112-1117, 1985.
16. Ermans AM: Prevention of iodine deficiency disorders by oral iodized oil. Eur J Endocrinol 130: 545-546, 1994.
17. Hetzel BS, Potter BJ, Dulberg EM: The iodine deficiency disorders: nature, pathogenesis and epidemiology. World Rev Nutr Diet 62: 59-119, 1990.
18. Hetzel BS: Iodine and neuropsychological development. J Nutr 130 (2s suppl): 4935-4955, 2000.
19. Potter JD, McMichael AJ, Hetzel BS: Iodization and thyroid status in relation to stillbirths and congenital anomalies. Int J Epidemiol 8(2): 137-144, 1979.
20. Bleichrodt N, Born MP: A meta-analysis of research on iodine and its relationship to cognitive development. In: Stanbury JB, (ed.), The damaged brain of iodine deficiency, Cognizant Communication Corporation, pp. 195-200, 1994.
21. Pharoah POD, Buttfield IH, Hetzel BS: Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet I: 308-310, 1971.
22. Cobra C: Infant survival is improved by oral iodine supplementation. J Nutr 127(4): 574-578, 1997.
23. Fierro-Benitez R, Cazar R, et al: Effects on school children of the prophylaxis of mothers with iodized oil in an area of iodine deficiency. J Endocrinol Invest 11: 327-335, 1989.
24. Pharoah POD, Ellis SM, Ekins RP, Williams ES: Maternal thyroid function, iodine deficiency and fetal development. Clin Endocrinol 5: 159-166, 1976.
25. Braverman LE, Ingbar SH: Changes in thyroid function during adaptation to large doses of iodide. J Clin Invest 42: 1216-1231, 1963.
26. Stubbe P: Neonatal goiter and hypothyroidism due to iodine application in the mother. In: Hall R, Kobberling J, (eds.), Thyroid disorders associated with iodine deficiency and excess. New York: Raven Press, Serono Symposia 22: 359-364, 1985.
27. Theodoropoulos T, Braverman LE, Vagenakis AG: Iodide-induced hypothyroidism: a potential hazard during prenatal life. Science 205: 502-503, 1979.
28. Wolff J: Iodide goiter and the pharmacological effects of excess iodide. Am J Med 47: 101-124, 1969.
29. Wolff J: Excess iodide inhibits the thyroid by multiple mechanisms. In: Ekholm RE, Kohn LD, Wollman SH, (eds.), Control of the thyroid gland. New York: Plenum, pp. 211-244, 1989.
30. Galina MP, Arnet NL, Einhorn A: Iodides during pregnancy. An apparent cause of neonatal death. N Engl J Med 267: 1124-1127, 1962.
31. Corrilain B, Van Sande J, Dumont JE: Inhibition by iodide of iodide-binding to proteins: the "Wolff- Chaikoff" effect is caused by inhibition of H_2O_2 generation. Biochem Biophys Res Commun 154: 1287-1292, 1988.
32. Tonglet R, Bourdoux P, Tshilembi M, Ermans AM: Effect of low oral doses of iodized oil in the control of iodine deficiency in Zaire. N Engl J Med 326: 236-241, 1992.
33. Azizi F, Kimiagar M, Nafarabadi M, Yassai M: Current status of iodine deficiency disorders in the Islamic Republic of Iran. EMR Health Serv J 8: 23-26, 1990.
34. Azizi F, Kalani H, Kimiagar M, et al: Physical, neuromotor and intellectual impairment in non-cretinous schoolchildren with iodine deficiency. Int J Vit Nutr Res 65: 199-205, 1995.
35. Azizi F, Sarshar A, Nafarabadi M, et al: Impairment of neuromotor and cognitive development in iodine deficient schoolchildren with normal physical growth. Acta Endocrinol 129: 501-4, 1993.
36. Azizi F, Sheikholeslam R, Hedayati M, Mirmiran P: Sustainable control of iodine deficiency in Iran. J Endocrinol Invest, in press, 1993.
37. Kimiagar M, Yassai MB, Nafarabadi M, Samami B, Azizi

F: Endemic goiter in Boyer-Ahmad. Med J IR Iran 3: 27-29, 1989.

38. Pharoah POD, Connonlly KJ: Effect of maternal iodine supplementation during pregnancy. Arch Dis Child 66: 145-147, 1991.
39. Thilly C: Prevention of myxedematous cretinism with iodized oil during pregnancy. In: Ui N, et al., (eds.), Current problems in thyroid research. Amsterdam: Excerpta Medica, pp. 386-389, 1983.
40. Vanderpas J, Thilly CH: Endemic neonatal, infantile and juvenile hypothyroidism in Ulbangi, Northern Zaire: clinical consequences and prevention. In: Stanbury JB, (ed.) The damaged brain of iodine deficiency. New York: Cognizant Communication, pp. 209-224, 1994.
41. Ermans AM: Congenital hypothyroidism in developing countries. In : Burrow GN, Dussault JH, (eds.), Neonatal thyroid screening. New York: Raven Press, pp. 61-73, 1980.
42. Delange F, et al: Influence of dietary goitrogens during pregnancy in human on thyroid function of the newborn. In: Delange F, et al. (eds.), Nutritional factors involved in the goitrogenic action of Cassava. Ottawa: International Development Research Center, pp. 40-50, 1982.
43. Thilly C: Maternal, fetal, and juvenile hypothyroidism, birthweight, and infant mortality in the etiopathogenesis of the IDD spectrum in Zaire and Malawi. In: Stanbury JB, (ed.) The damaged brain of iodine deficiency. New York: Cognizant Communication, pp. 241-250, 1994.
44. Chaouki ML: Endemic cretinism and congenital hypothyroidism in endemic goiter in Algeria. In: Medeiros-Neto GA, Gaitan E, (eds.), Frontiers of thyroidology. New York: Plenum Press, pp. 1055-1060, 1986.
45. Berghout A, Endert E, Ross A, Hogerzeil HV, Smits NJ, Wiersinga WM: Thyroid function and thyroid size in normal pregnant women, living in an iodine replete area. Clin Endocrinol 41: 375-9, 1994.
46. Kochupillai N, Pandav CS: Neonatal chemical hypothyroidism in iodine-deficient environments. In: Hetzel BS, Dunn JT, Stanbury JB, (eds.), The prevention and control of iodine deficiency disorders. Amsterdam: Elsevier, pp. 85-93, 1987.
47. Kochupillai N: Prevention and control of goiter. Demerits of iodized oil injections. Bull Nutr Found India 12: 1-5, 1991.
48. Kochupillai N, Godbole MM, Pandav CS, Mithal A, Ahuja MMS: Environmental iodine deficiency, neonatal clinical hypothyroidism (NCH) and iodized oil prophylaxis. In: Kochupillai N, Karmakar MG, Ramalingasawami V, (eds.), Iodine nutrition, thyroxine and brain development. Tata McGraw-Hill Publications, New Delhi, pp. 87, 1986.
49. Coppens M, Swennen B, Moreno-Reyes R, Thilly C: Entire prevention of neonatal hypothyroidism but shorted responsiveness to oral iodized oil during pregnancy (Abstract). The Fourth International Congress on Endocrine Disorders, November 20-22, Tehran, Iran, O22, 1996.