Infant Survival Is Improved by Oral Iodine Supplementation[1,2]

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ABSTRACT Although reports suggest that infant mortality is increased during iodine deficiency, the effect of iodine supplementation on infant mortality is unknown. A double-masked, randomized, placebo-controlled, clinical trial of oral iodized oil was conducted in Subang, West Java, Indonesia to evaluate the effect of iodine supplementation on infant mortality. Infants were allocated to receive placebo or oral iodized oil (100 mg) at about 6 wk of age and were followed to 6 mo of age. Six hundred seventeen infants were enrolled in the study. Infant survival was apparently improved, as indicated by a 72% reduction in the risk of death during the first 2 mo of follow-up ($P < 0.05$) and a delay in the mean time to death among infants who died in the iodized oil group compared with infants who died in the placebo group (48 days vs. 17.5 d, $P = 0.06$). Other infant characteristics associated with reduced risk of death included weight-for-age at base line, consumption of solid foods, female gender and recent history of maternal iodine supplementation. Oral iodized oil supplementation had a stronger effect on the mortality of males compared with females. This study suggests that oral iodized oil supplementation of infants may reduce infant mortality in populations at risk for iodine deficiency. J. Nutr. 127: 574–578, 1997.

KEY WORDS: • *infants* • *mortality* • *iodine deficiency* • *goiter* • *cretinism*

Approximately 1.6 billion people worldwide may consume inadequate daily amounts of iodine (UNICEF 1995) and are at risk for iodine deficiency disorders (IDD)[4] (Hetzel and Pandav 1994), which include enlargement of the thyroid (goiter) and a wide spectrum of mental, psychomotor and growth abnormalities (Delange 1994). Currently, there are an estimated 655 million cases of endemic goiter and 26 million cases of preventable mental deficiency, including 5.7 million cases of cretinism worldwide (Hetzel and Pandav 1994, WHO 1991b). Seventy-five percent of people with goiter live in developing countries (Gaitan et al. 1991). In areas with a high prevalence of IDD, maternal and fetal iodine deficiency has been associated with increased rates of stillbirth, abortion, congenital anomaly, and infant mortality (Pharoah et al. 1976, Thilly et al. 1980). Iodine supplementation of women before conception or during pregnancy seems to reduce abortions, stillbirths and infant mortality (Chaouki and Benmiloud 1994, Fierro-Benitez et al. 1988, Glinoer et al. 1995, Hetzel 1983, Pharoah and Connolly 1987, Pharoah et al. 1971 and 1972, Potter et al. 1979). Although these studies suggest that iodized oil supplementation of infants might improve their survival, this has not been shown definitively.

Oral iodized oil supplementation might influence infant survival through its effect on thyroid status and immunity. Thyroid hormones exert a powerful modulating effect on the immune system (Fabris 1973), including effects on B cell differentiation (Paavonen 1982), antibody responses (Keast and Ayre 1980), lymphoproliferation to mitogen (Keast and Taylor 1982) and T cell subsets (Ohashi and Itoh 1994). Although the relationship between thyroid disease and autoimmunity is well documented (Mooij and Drexhage 1992), less is known regarding IDD and immune function in humans. Thyroid status and vitamin A status may also potentially interact to modulate immune responses. Both an active metabolite of vitamin A, 9-*cis* retinoic acid, and thyroid hormone can bind to retinoid X receptor (Leng et al. 1994) and control gene transcription.

SUBJECTS AND METHODS

The study population consisted of mothers and their infants from 28 villages in an area of mild-to-severe IDD in Subang, West Java, Indonesia. Eligible infants were 6–10 wk old, clinically euthyroid, and born in the study villages. The time of supplementation of 6–10 wk of age was based upon the possible programmatic integration of oral iodized oil supplementation with the first visit of the Expanded Programme on Immunization (EPI) (Bruning et al. 1993, WHO 1987, 1990 and 1991a) at which time infants received oral poliovirus and diphtheria-pertussis-tetanus vaccines. The study design was a randomized, double-masked, placebo-controlled, clinical trial. Infants were allocated by random number table in blocks of 10 to receive oral

iodized oil or placebo, which was given at the first EPI visit. Upon enrollment, infants were assigned sequential identification numbers. An envelope labeled with the identification number contained identically appearing capsules of either oral iodized oil in poppyseed oil (100 mg) or poppyseed oil placebo (Lipiodol, Laboratoire Guerbet, Aulnay-sous-bois, France). The code was unknown to the investigators and study team until after the completion of the study. The capsules were administered immediately after the first dose of oral polio vaccine. Infants in the clinical trial then completed the immunization schedule of the EPI with visits at 10 and 14 wk of age, and a final follow-up evaluation at 6 mo of age.

A 7-d morbidity history was obtained at each visit. Height, weight, mid-upper arm circumference and head circumference were assessed at the first, third and final visits using standard procedures. At each visit, mothers were asked whether their infants were being breast-fed and/or given solid food or other liquids besides breastmilk, how many times a day they were breast-fed and/or fed other foods, and the list of other foods given. Community health workers visited the homes of participants on a monthly basis and monitored the study population for deaths, including those among infants who dropped out of the study but remained in their villages. Probable causes of death were determined by the pediatrician after interviewing relatives of the deceased infant using verbal autopsy techniques adapted from other pediatric studies (Dowell et al. 1993, Kalter et al. 1990).

Base-line and follow-up comparisons between treatment groups were made using Student's t test for comparison of two means and Fisher's exact test for comparison between proportions, with statistical significance at a two-tailed P value of 0.05 or less. Absolute and gender-stratified relative risk, mortality rates and Kaplan-Meier survival curves were calculated and compared between allocation groups (Armitage and Berry 1987). Adjusted survival analyses were conducted using Cox regression models (Kleinbaum et al. 1982). Written informed consent was obtained from parents or guardians. The study was approved by the institutional review board at the Johns Hopkins School of Medicine and by the ethical committees of the Hasan Sadikin Hospital, University Pajajaran and the Ministry of Health, Government of Indonesia.

RESULTS

From June to October 1994, 617 infants were recruited to participate in the study. Of the 617 participants, 307 (49.8%) infants received oral iodized oil and 310 (50.2%) received placebo; 311 (50.4%) infants were males and 306 (49.6%) were females. The treatment groups were similar by maternal goiter status, maternal age, infant gender, socioeconomic status, use of iodized salt and all other characteristics at base line, some of which are displayed on **Table 1.** Five hundred seven infants completed follow-up to 6 mo, 255 of 307 in the iodized oil group (83%), and 252 of 310 (81%) in the placebo group. There was no differential loss to follow-up by treatment group or gender. Eighty-eight infants dropped out of the study before 6 mo of age. Their base-line characteristics were similar to those who remained in the study (data not shown). A total of 22 infants died, 15 (68.2%) in the placebo group and 7 (31.8%) in the iodized oil group. Of those who died, 14 (63.6%) were male and 8 were female (36.4%).

Infants who died before 6 mo of age were significantly lighter and had smaller head and arm circumferences at study entry than the infants who survived to 6 mo of age. Their mean weight-for-age was also significantly lower, indicating that they were malnourished at base line in comparison with the surviving infants (**Table 2**). None of the mothers whose infants died had a history of iodized oil supplementation in comparison with 86 (17%) of the 507 mothers whose infants survived to 6 mo of age ($P = 0.034$). Supplemented mothers had received oral iodized oil on average 120 d before the beginning of the study. No other base-line differences were observed between those who survived to 6 mo of age and those who did not. The percentage of mothers who had been

supplemented in the past and the time elapsed between maternal and infant supplementation were similar in the iodized and placebo groups.

Deaths in the iodized oil group occurred on average 48 d ($\pm$ 13.1) after the intervention, whereas in the placebo group, deaths occurred on average 17.5 d ($\pm$ 4.0) after the initial visit ($P = 0.06$). There were 13 deaths (65%) due to pneumonia or bronchopneumonia, 1 death (5%) due to meningoencephalitis, 1 death (5%) due to asphyxia, and 2 deaths with unspecified diagnoses (allergic reaction and shock of undetermined nature). Five deaths were not investigated through verbal autopsies. The unadjusted relative risk of death in the iodized oil group in comparison with the placebo group during the first 1, 2 and 4 mo of follow-up were 0.19 (95%CI 0.04–0.85, $P = 0.021$); 0.28 (95%CI 0.09–0.82, $P = 0.018$); and 0.48 (95%CI 0.20–1.15, $P = 0.126$), respectively. **Figure 1** shows the Kaplan-Meier survival curves according to treatment group. At the end of 4 mo of follow-up, the overall mortality experience in the iodized oil group was still considerably lower than that of the placebo group, corresponding to a 52% reduction in mortality in the supplemented group. The final mortality difference at 6 mo of age, however, failed to reach statistical significance, perhaps due to the small sample size studied. The power to detect a difference such as the one observed at 6 mo of age was approximately 32%.

Multivariable Cox regression analysis was used to measure the effect of other independent variables on survival, to control for potential confounding and to test for interactions. Variables analyzed included gender, infant's diet at base line (breastfeeding and/or introduction of solid foods), diarrhea or acute respiratory infection (cough, difficult breathing, or fast breathing) at base line, history of maternal iodized oil supplementation, anthropometry at base line, and interaction among treatment, gender and other variables showing association with survival. Iodine supplementation, consumption of solid foods or liquids at base line, female gender, weight, weight-for-age Z-score (WAZ), and head and arm circumference were independently associated with improved survival. WAZ was selected for the final model on the basis of the magnitude and statistical significance of the beneficial effect on survival and multicolinearity between anthropometric parameters. **Table 3** presents the results of the multivariable Cox survival analysis with the effect of iodine supplementation adjusted for gender, WAZ and consumption of solid foods at base line. Treatment effect was not confounded and did not interact with the effect of solid foods and anthropometry at base line. Sex-stratified analysis of treatment effect indicated that male survival at 6 mo of age in the iodized oil group was significantly better than that of male infants in the placebo group (22.9 per 1000 vs. 84.6 per 1000, $P = 0.03$). The P-value for the interaction between treatment and sex in the Cox regression model was 0.15. Because the difference in mortality occurred soon after enrollment, there were limited data regarding time-dependent variables such as anthropometry and diet for the infants who died; therefore, the Cox regression analysis was limited to base-line variables only.

Among 326 infants whose base-line diets included foods or liquids, 164 (50.0%), 126 (38.4%), 35 (11.3%) and 1 (0.3%) were fed solid foods or liquids 1, 2, 3 and 4 times/d, respectively. Other liquids consisted of water, tea with sugar or honey, or fruit juice. Solid or mushy foods included premasticated rice (bubur), mashed bananas, biscuits, industrialized infant food (e.g., Promina and Farley) and infant formulas (e.g., Lactogen, SNN and SGN). The proportion of infants breast-fed at base line was lower, but not significantly so, among infants who received supplements (95.7 vs. 97.9%, $P = 0.125$). Infants who received solid foods or liquids supplements at base line were slightly, but significantly older at study

TABLE 1

Selected base-line characteristics by allocation group

	Placebo $n = 310$ n (%)	Iodized oil $n = 307$ n (%)	*P*-value
Maternal characteristics			
Goiter grade[1]			
00	275 (89.6)	267 (87.6)	0.54
1A	20 (6.5)	26 (8.5)	
1B	7 (2.3)	8 (2.6)	
02	3 (1.0)	4 (1.3)	
03	2 (0.6)	0 (0.0)	
Previous maternal iodine supplementation	52 (16.8)	47 (15.3)	0.66
Use of vitamin and mineral supplements during pregnancy	259 (84.6)	261 (85.6)	0.82
Mean age,[1,2] *y*	25.4 ± 0.32	25.7 ± 0.32	0.61
Pregnancies, *n*	2.3 ± 0.09	2.3 ± 0.08	0.69
Deliveries, *n*	2.2 ± 0.09	2.2 ± 0.08	0.76
Live births, *n*	2.2 ± 0.09	2.2 ± 0.08	0.69
Children alive, *n*	2.1 ± 0.08	2.1 ± 0.07	0.98
Maternal education, *y*	7.1 ± 0.15	7.4 ± 0.16	0.32
Maternal occupation: housewife	272 (94.1)	266 (90.5)	0.32
Infant gender, age at base line, and delivery history			
Gender			
Male	157 (50.6)	154 (50.2)	0.90
Female	153 (49.3)	153 (49.8)	
Place of delivery			
Home	269 (86.8)	272 (89.2)	0.66
Midwife's house	16 (5.1)	11 (3.6)	
Hospital	17 (5.5)	17 (5.6)	
Clinic	8 (2.6)	5 (1.6)	
Delivery assisted by			
Traditional birth attendant	235 (76.1)	237 (77.5)	0.38
Midwife	65 (21.0)	65 (21.2)	
Doctor	9 (2.9)	4 (1.3)	
Mean birth weight, *kg*[1]	3.20 ± 0.03	3.20 ± 0.03	0.74
Mean age, *mo*	1.82 ± 0.02	1.80 ± 0.02	0.54

[1] Data from placebo group ($n = 307$), iodized oil group ($n = 305$).
[2] Mean ± SEM.

entry than infants who did not receive supplements (1.9 vs. 1.8 mo, $P < 0.0001$). They were also heavier and taller (4.9 vs. 4.7 kg, $P = 0.0041$; 56.2 vs. 55.5 cm, $P = 0.0003$), had slightly greater head and arm circumference (38.0 vs. 37.7 cm, $P = 0.002$; and 12.5 vs. 12.4 cm, $P = 0.05$), but similar age adjusted Z-scores (WAZ 0.03 vs. −0.03, $P = 0.371$; height-for-age Z-score −0.34 vs. −0.45, $P = 0.109$; weight-for-height Z-score 0.37 vs. 0.39, $P = 0.622$). Infants who did not receive solid foods were more likely to have a better socioeconomic status as indicated, for instance, by the significantly higher percentage living in houses with electricity and higher mean

years of parental schooling (data not shown). The effect of supplemental foods/liquids on survival did not change when controlled for age, socioeconomic status, iodine supplementation, WAZ or gender.

DISCUSSION

This study suggests that iodine (100 mg) given at 6 wk of age may reduce the risk of death among infants in a geographi-

TABLE 2

Birth weight and base-line age and anthropometry by infant vital status

	Dead $n = 22$	Alive $n = 507$	*P*-value
Birthweight,[1,2] *kg*	3.0 ± 0.11	3.2 ± 0.02	0.10
Age at base line, *mo*	1.7 ± 0.07	1.8 ± 0.01	0.32
Weight, *kg*	4.5 ± 0.14	4.8 ± 0.03	0.03
Length, *cm*	55.0 ± 0.49	55.8 ± 0.11	0.12
Head circumference, *cm*	37.2 ± 0.24	37.9 ± 0.06	0.01
Arm circumference, *cm*	11.9 ± 0.21	12.5 ± 0.05	0.02
Weight-for-age Z-score	−0.43 ± 0.17	0.03 ± 0.04	0.01
Height-for-age Z-score	−0.70 ± 0.20	−0.38 ± 0.04	0.09
Weight-for-height Z-score	0.16 ± 0.17	0.40 ± 0.03	0.11

[1] Mean ± SEM.
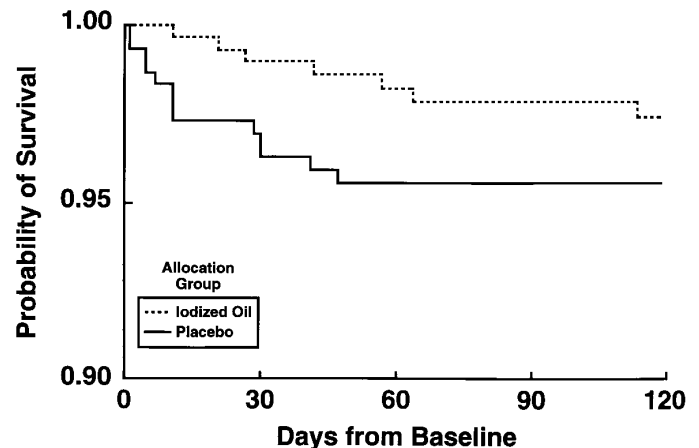[2] For birthweights, those who died ($n = 17$), those alive ($n = 331$).

FIGURE 1 Survival of infants in the oral iodized oil and placebo groups from time of supplementation through 120 d of follow-up. Age at base line was 6 wk.

TABLE 3

Relative risk (RR) of death and 95% confidence interval (CI) at 1, 2 and 4 mo after study entry according to iodine supplementation adjusted for gender, weight-for-age Z-score and consumption of solid foods at base line

Variable	1 mo	2 mo	4 mo
	RR (95% CI; *P*)	RR (95% CI; *P*)	RR (95% CI; *P*)
Iodized oil vs. control	0.20 (0.04–0.91; 0.04)	0.30 (0.10–0.90; 0.03)	0.52 (0.21–1.28; 0.15)
Solid food vs. no solid food	0.41 (0.12–1.35; 0.14)	0.41 (0.15–1.09; 0.08)	0.41 (0.17–1.01; 0.05)
Female vs. male	0.54 (0.18–1.68; 0.29)	0.39 (0.15–1.04; 0.06)	0.49 (0.20–1.18; 0.11)
Weight-for-age Z-score at base line	0.58 (0.30–1.13; 0.11)	0.53 (0.30–0.92; 0.02)	0.55 (0.33–0.91; 0.02)

cal area of iodine deficiency. The absence of deaths among infants whose mothers received iodine supplementation in the recent past was another finding in this study that also supports the potentially beneficial role of iodine in reducing mortality. To our knowledge, this is the first study to demonstrate that infant oral iodine supplementation can reduce infant mortality. This finding is corroborated by previous studies that suggest that infant survival is improved among infants born to women whose iodine deficiency was corrected before or during pregnancy. In Algeria, the rates of abortion, stillbirth and prematurity were significantly lower among women treated with oral iodized oil 1–3 mo before conception or during pregnancy than among untreated women (Chaouki and Benmiloud 1994). Infant mortality was lower among infants born to women who received intramuscular iodized oil supplementation at around 28 wk of pregnancy compared with infants born to controls in a clinical trial from Zaire (Thilly et al. 1980). Studies in Papua New Guinea indicated an inverse relationship between levels of maternal thyroxine during pregnancy and death rates among the offspring (Pharoah et al. 1976), and an improved long-term survival among children born to women whose iodine deficiencies were corrected during or shortly before pregnancy (Pharoah and Connolly 1987). A possibly related finding is a recent report of significantly reduced mortality among young sheep in villages receiving iodine in irrigation water compared with control villages in China (Cao et al. 1994).

This study suggests that there may be a possible differential effect of treatment according to gender. Nutritional and immunological differences between boys and girls may influence response to infections and survival. For example, boys are more susceptible to vitamin A deficiency than girls, which is a consistent observation in different countries (Sommer 1982). Differences in immunologic status (Leon et al. 1993), responses to vaccination (Garenne et al. 1991) and micronutrient supplementation (Sazawal et al. 1996) are known between boys and girls. It is unknown whether boys are at higher risk of iodine deficiency or whether there is a gender difference in response to iodine supplementation. A treatment effect may not have been observed in girls because of their already high survival rate of 97%.

It is possible that infants receiving solid foods were exposed to commercial products which potentially provided them with additional sources of iodine. However, the study did not use systematic methodologies carefully designed for the evaluation of dietary practices or for adequate assessment of iodine content of foods. The finding of improved survival among infants having solid foods in the diet at study entry should be investigated further by means of a more precise dietary assessment. This study is limited in that biochemical indicators of iodine and thyroid status were not available. However, detailed anthropometric evaluation and clinical assessment of maternal goiter suggest that the observed differences in mortality were not due to base-line imbalances in the treatment group.

Traditionally, the main focus in the prevention of IDD has been to eliminate the ensuing mental impairment, cretinism and goiter. Ideally, adequate iodine levels should be made available from the beginning of fetal development in utero by adequate supplementation of women of childbearing age and pregnant women. The EPI may serve as an additional delivery system for providing supplementation to mothers and infants who missed earlier opportunities. The duration for which one 100-mg dose of iodine will correct iodine deficiency in a 6-wk-old infant is unknown; however, WHO (1991) estimates that a 240-mg dose of iodine administered once in the first year of life will correct iodine deficiency for up to 2 y. Infant iodine supplementation may be a potential intervention that could reduce infant mortality in iodine-deficient areas by 50%; further study is required to corroborate these findings with a larger sample size. Iodine supplementation may be an important strategy for child survival, and this study suggests that the infrastructure to deliver supplements could be provided by the Expanded Programme on Immunization.

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