

PREVENTING AND TREATING IODINE DEFICIENCY

Prevalence of Iodine Deficiency

Iodine Deficiency Disorders (IDD) have multiple and serious adverse effects including cretinism, goitre, impaired cognitive function, impaired growth, infant mortality, LBW, and stillbirths in a large proportion of the world's population. The degree of impairment in function is related to the severity of iodine deficiency. Even marginal degrees of iodine deficiency have a measurable impact on human development. There has been great progress in prevention and treatment of IDD in the last decade. The obvious need for interventions probably explains why there have been relatively few randomized, placebo-controlled trials of the efficacy of iodine supplementation on different aspects of human function.

The most commonly used indicators (Table 9) are: enlarged thyroid volume: prevalence of goitre, or total goitre rate (TGR); enlarged thyroid gland; urinary iodine; and elevated neonatal serum levels of thyroid stimulating hormone (TSH). Iodine deficiency is defined as endemic when it affects more than 10% of the population.

In 1993, the estimated TGR in school children in some Asian countries was, in descending order of prevalence: Nepal, 44%; Indonesia, 28%; Bhutan,

25%; Myanmar, 18%; Republic of Korea, 15%; Sri Lanka, 14%; Thailand, 12%; Bangladesh, 11%; India, 9%; and Mongolia, 7%³⁷⁰.

In 1999, WHO, UNICEF and the International Coordinating Committee on Iodine Deficiency Disorders (ICCIDD) classified 130 out of 191 countries as having IDD problems, 20 as having eliminated IDD problems and the remainder as having an unknown level of IDD problems¹¹. About 172 million people, or 12% in South-East Asia, are affected by goitre and 41% are at risk of goitre, and have probably been affected by marginal iodine status. There has been little change in this situation in the past decade although improvement is anticipated now that 70% of households in South-East Asia consume iodized salt¹¹.

Causes of Iodine Deficiency

The main cause of iodine deficiency in soils is leaching by glaciation, floods or high rainfall. Mountainous regions including the Andes and the Himalayas therefore have some of the highest prevalences of iodine deficiency. Iodine deficiency also occurs due to flooding; for example, in Bangladesh and in India around the Ganges. In areas of endemic iodine deficiency, the water and foods (plants and animals grown there) have low iodine content.

TABLE 9: Indicators for prevalence of iodine deficiency disorders (IDD) as public health problems

Indicator	Normal	Mild IDD	Moderate IDD	Severe IDD
% Goitre in school children	<5	5-19.9	20-29.9	>30
% Thyroid volume in school children >97 th percentile	<5	5-19.9	20-29.9	>30
Median urine iodine (µg/L)	100-200	50-99	20-49	<20
% Neonatal thyroid stimulating hormone (TSH) >5 µU/mL blood	<3	3-19.9	20-39.9	>40

Source: Delange F (1999) Neonatal thyroid screening as a monitoring tool for the control of iodine deficiency. *Acta Paediatrica*, Supplement 88 (432): 21 – 24.

Many staple foods consumed in developing countries contain cyanogenic glucosides that can liberate cyanide. Cyanide is converted to thiocyanate in the body. This is a goitrogen, as it blocks the uptake of iodine by the thyroid. With the exception of cassava, cyanogenic glucosides are located in the inedible portion of plants. Cassava, however, must be soaked before consumption to remove the goitrogens. Consumption of cassava was associated with endemic goitre and cretinism in Sarawak, Malaysia³⁷¹. The adverse effects can also be overcome by increasing iodine intake.

Selenium is an essential component of the enzyme, type I deiodinase, which catalyzes the conversion of thyroxine (T_4) to triiodothyronine (T_3)³⁷². Combined iodine and selenium deficiencies are thought to cause the myxoedematous form of goitre, which is found in central D.R. of Congo and other locations³⁷³. Low selenium areas include parts of Australia, the PRC, Egypt and New Zealand. High selenium intakes, such as encountered in some regions of Venezuela, also affect thyroid function by reducing the production of T_3 from T_4 ³⁷⁴.

Iron deficiency impairs thyroid hormone metabolism because the two first steps in thyroid hormone synthesis are catalyzed by thyroperoxidases, which are iron requiring enzymes. Iron deficiency lowers plasma T_3 and T_4 concentrations, reduces the rate of conversion of T_4 to T_3 , and increases thyrotropin concentrations. Because of these impairments in iodine metabolism, goitre in anaemic individuals may be less responsive to iodine treatment. At 30 weeks after the administration of oral iodine to children in Côte d'Ivoire, the prevalence of goitre was 64% in anaemic, iron deficient individuals and 12% in those with adequate iron status³⁷⁵. The inclusion of an iron supplemented group would have made the conclusions more definite, but these results indicate that combining iodine with iron supplements might reduce goitre more rapidly than iodine alone.

Consequences of Iodine Deficiency Disorders

Cretinism

Cretinism is the result of iodine deficiency during pregnancy, which adversely affects foetal thyroid function. Normal concentrations of thyroid hormone are needed for normal foetal brain development. The foetal brain is probably damaged when there is iodine deficiency during the first trimester. Neurological cretinism is characterized by poor cognitive ability, deaf mutism, speech defects, and proximal neuromotor rigidity. It occurs where

iodine intake is below about 25 $\mu\text{g}/\text{day}$. It is much more prevalent than myxoedematous cretinism which includes hypothyroidism with dwarfism.

Goitre

The prevalence of goitre increases with age and it peaks during adolescence. Prevalence is higher in boys than in girls. The rate of goitre in school children aged 8 to 14 years is a convenient way to assess the iodine status of a community (Table 9). Goitre itself is unsightly but usually harmless. Importantly, its presence indicates that other damaging effects of iodine deficiency are already present.

Impaired Cognitive Function

Iodine deficiency is the leading cause of preventable mental retardation and brain damage worldwide. Differences in psychomotor development of iodine deficient children become apparent after the age of about 2.5 years. A comparison of learning ability and motivation was carried out among children, aged 9 to 15 years, in severely and mildly iodine deficient communities in Uttar Pradesh, India³⁷⁶. Children from the severely iodine deficient villages learned more slowly and were less motivated to achieve. In rural Bangladesh, children with low T_4 levels performed less well than those with normal levels, in tests of reading, spelling and general cognitive ability, after a number of other factors that affected performance were statistically controlled³⁷⁷. Even lesser degrees of iodine deficiency, which affect many more individuals, can impair mental and motor function. Problems range from small neurological changes, to impaired learning ability and performance in school, and poor performance on formal tests of psychomotor function³⁷⁸. A meta-analysis of 18 studies, on a total of 2,214 subjects, showed that mean cognitive and psychomotor performance scores were 13.5 IQ points lower in iodine deficient individuals³⁷⁹. The problem of retarded neurological development is exacerbated by the many individuals in the affected child's social environment who will also be dull, apathetic and unmotivated as a result of iodine deficiency.

Increased Perinatal Morbidity and Mortality

Maternal iodine deficiency during pregnancy is associated with a higher incidence of stillbirths, abortions and congenital abnormalities. These can be reduced by maternal iodine supplementation before or during pregnancy. In Papua New Guinea in 1976, the rate of perinatal deaths for mothers with very low serum T_4 concentrations was twice that of those with

higher concentrations³⁸⁰, perhaps because thyroid hormones have a strong modulating effect on the immune system.

Iodine Efficacy Trials

Approaches to reduce iodine deficiency have been reviewed in detail². The most widely used method is salt iodization. Universal salt iodization (USI), where 80% of the population must have access to iodized salt, has been adopted by India and many other countries. Another strategy is injection of iodized oil. This is particularly appropriate for isolated regions and where salt is not iodized. A dose (480 mg iodine in 1 mL of poppy seed oil) lasts about 4 years. It should be given to all females up to age 40 years and to all males up to age 20 years. Repeat injections are needed after 3 to 5 years. Alternative strategies, such as adding iodine to drinking water (Thailand and Malaysia)³⁸¹ or to irrigation water in the PRC³⁸², show promise. The latter strategy has the advantage that it can improve also the growth of plants and animals in areas of endemic iodine deficiency.

Effects on Goitre Reduction

Salt iodization programmes do not always have an immediate impact on the prevalence of goitre. For example, in the Republic of South Africa, the prevalence of goitre in children did not decline after 12 months of mandatory salt iodization³⁸³. However, in this and many other similar situations, noniodized salt was still being consumed by some of the households. In contrast, after iodized salt was introduced into the northern village of Jixian in the PRC in 1978, the prevalence of goitre fell from about 65% to 4% in the next 4 years, and no cretins were born during that period³⁸⁴. Groups of school children in the PRC were supplied with iodized salt (25 ppm iodine which is equivalent to 42.25 g potassium iodate per kg of salt), iodized salt purchased in the market, or a 400 mg iodine dose in oil. Goitre prevalence was 18% at baseline. It fell to 5% within 12 months in the children supplied with iodized salt or oil, and to 9% in 18 months in the group who purchased iodized salt in the market³⁸⁵.

School children aged 6 to 11 years in the Republic of South Africa were provided with biscuits fortified with iodine, as well as iron and beta-carotene, for 43 weeks. The biscuits supplied 60 µg iodine per day. The prevalence of low urinary iodine concentrations fell from 97 to 5%. However, there was no reduction in the prevalence of goitre, which was about 20% at

the beginning and at the end of the study³⁸⁶. These authors concluded that iodine status had improved but that more time was needed to reduce goitre size. The implication from these observations is that urinary iodine concentration is a more sensitive indicator for monitoring the effectiveness of programmes intended to lower the risk of iodine deficiency in a population group.

Effects on Pregnancy Outcome

The injection of iodized oil before pregnancy can prevent endemic cretinism. This has been confirmed in: Papua New Guinea³⁸⁷; the D.R. Congo³⁸⁸; and Peru³⁸⁹. Programmes to inject iodized oil prevented endemic cretinism in the PRC³⁹⁰ and Indonesia³⁹¹. An analysis of clinical outcomes in maternal iodine supplementation trials⁹⁷ included three studies on a total of 1,551 women^{98, 99, 392}. In two of these, in the D.R. Congo and in Papua New Guinea, there was a significant reduction in the mortality of infants and young children. Iodine supplementation also lowered the prevalence of endemic cretinism at the age of four years, and the supplemented children had better psychomotor function between 4 and 25 months of age.

Iodized oil given in the first and second trimester of pregnancy protects against cretinism, but has little effect when given in the third trimester. This was studied in a severely iodine deficient area in Xinjiang, PRC³⁹³. Iodine was delivered systematically to women, in each trimester of pregnancy, and to groups of children from birth to age 3 years. For the 120 infants whose mothers were given iodine in the first or second trimester, the prevalence of moderate or severe neurologic abnormalities was 2%, compared to 9% in the 752 who received iodine through their mother in the third trimester, or postnatally. Outcomes were best when treatment was given during the first trimester. However, treatment in late pregnancy or postnatally improved brain growth and developmental quotients slightly, but not neurologic status compared to untreated children.

Belgian women with mild iodine deficiency, selected at the end of their first trimester of pregnancy if they had biochemical evidence of excessive thyroid stimulation, responded to daily iodine doses with markedly suppressed thyroid hormone levels and less increase in thyroid volume compared to a placebo group³⁹². The thyroid volume of their newborn infants was also smaller. Given the critical nature of iodine status and normal thyroid hormone levels during pregnancy, it is evident that monitoring of maternal iodine status is worthwhile, even in areas of mild iodine deficiency.

Effects on Infant Mortality

Iodine supplementation during pregnancy results in a substantial reduction in foetal and neonatal deaths. In the D.R. Congo, injection of iodized oil in the last half of pregnancy reduced perinatal and infant mortality and improved birthweight³⁸⁸. Moreover, in Papua New Guinea, children born to pregnant mothers who received iodine were significantly faster and more accurate in tests of manual function, when evaluated and compared to controls 12 years later³⁹⁴.

A randomized, placebo-controlled, clinical trial of oral iodized oil in West Java, Indonesia was designed to determine the effect of giving iodine (100 mg), at about 6 weeks of age, on infant mortality up to 6 months of age³⁹⁵. There was a 72% reduction in risk of mortality in the iodized oil group compared to the placebo group, during the first 2 months, and a delay in the mean time to death: 48 days compared to 17 days. The effect on mortality was strongest in male infants. These results illustrate the importance of correcting iodine deficiency, *in utero* and in early life. The WHO estimates that giving a 240 mg dose of iodine once in the first year of life can prevent iodine deficiency for as long as two years. The EPI might offer one opportunity to provide this dose.

The prevalence of elevated serum TSH concentrations (>5 mU/L blood) in cord blood is a sensitive index of iodine deficiency at the population level³⁹⁶ and can also serve to detect iodine deficient infants at birth. In the late 1990s, the prevalence of elevated neonatal TSH was <4% in areas with adequate iodine nutrition, compared to close to 30% in moderate IDD regions (e.g., 32% in Manila) and 39 to 80% where IDD is severe (including the PRC, Georgia, the Kyrgyz Republic, Malaysia, Thailand, and Pakistan)³⁹⁶.

Effect on Child Growth

There have relatively few trials of the impact of iodine supplementation on the growth of iodine deficient children, although such children are often small. In Bolivia, supplementation of 100 goitrous school children, aged 5.5 to 12 years, with a 475 mg oral dose of iodine in oil, showed no impact on growth during the subsequent 22 months compared to controls²⁷⁰.

Effects on Children's Cognitive Function

There have been few randomized, placebo-controlled trials of the effects of iodine supplementation on cognitive function in children. Improvement in the IQ score of goitrous school children in Colombia was correlated with goitre reduction and urinary iodine, although this was independent of oral iodine supplementation: not only iodine supplementation groups but also the control group received iodine from some sources during the 22-month study²⁷⁰. In Ecuador, 51 children, aged 6 to 10 years, from an iodine deficient community were injected with iodized oil and followed up 2 years later. Compared with a nonintervention group in a different village (there was no placebo control), treated girls, but not boys, performed better on intelligence tests³⁹⁷. In Malawi, a double-blind, placebo-controlled study found no effect on motor or mental development when 6 to 8-year-olds were supplemented in an area of endemic goitre³⁹⁸. This study has been criticized however, because there was a 25% dropout of participants. A joint Pan America Health Organization (PAHO) World Bank review of this question concluded that: *"the data from childhood supplementation studies are less clear than those from maternal supplementation studies, probably because so few studies have been undertaken with this design."*^a Clearly additional studies are needed on the benefits of iodine supplementation during childhood on psychomotor performance.

Potential for Iodine Toxicity

Biochemical and even clinical signs of hyperthyroidism have been reported in two severely iodine deficient African countries, Zimbabwe and the D.R. Congo, soon after the introduction of iodized salt. These two countries also had access to iodized salt imported from other countries³⁹⁹. Elderly persons, with long standing nodular goitre, appear to be the most susceptible to iodine-induced hyperthyroidism⁴⁰⁰. Clearly, careful monitoring of the iodine content in commercial salt is necessary, accompanied by reporting of cases of thyrotoxicosis, especially after the recent iodization of salt. The public health benefits of salt iodization, however, far outweigh risks from toxicity.

^a Bank PW (1999) *Nutrition, Health and Child Development. Research Advances and Policy Recommendations*. Washington DC: Pan-American Health Organization.

Summary and Conclusions

Iodine deficiency is a serious problem in Asia, with the prevalence in South-East Asia exceeding that in all other regions of the world. The need to eliminate iodine deficiency is very clear based on the widespread damaging effects and the large number of people affected. This may explain why there are so few randomized, placebo-controlled trials of the effects of iodine supplementation on the function of population groups. The following conclusions are justified based on existing trials.

- Salt iodization is by far the most important population-based intervention for IDD control and has been shown to be efficacious in alleviating IDD assuming iodine concentrations in the salt are at appropriate levels at the time of consumption.
- Efforts toward establishing and sustaining national salt iodization programmes have accelerated over recent years. Effective partnerships have been forged between relevant UN agencies, national and international NGOs, and the salt industry. Globally, 68% of households in countries with IDD consume iodized salt. Iodization rates are 70% in South-East Asia and 76% in the Western Pacific (WHO regions). These figures reflect household survey data where this is available; otherwise production level data are used as a proxy.
- Cretinism results from maternal iodine deficiency during pregnancy. It can be prevented by supplementing the mother during pregnancy, preferably during the first trimester but no later than the second trimester. Supplementation in late pregnancy, if that is the first time the mother can be reached, may provide some small benefits for infant function.
- Iodine deficiency during early life adversely affects learning ability, motivation, school performance and general cognitive function. It is not yet clear whether iodine supplementation benefits cognitive function if started during childhood. More studies are needed on this question. Neither is it clear whether supplementation improves growth of children.
- In an iodine deficient region, iodine supplementation even in the last half of pregnancy substantially reduced infant mortality and improved birthweight.
- Giving iodized oil to 6-week old infants caused a 72% reduction in mortality in the first two months. This suggests that it may be useful to administer iodized oil to young infants in areas where iodine deficiency is prevalent, although more studies of this question are needed.

