Systematic review of the effects of iodised salt and iodised oil on prenatal and postnatal growth

Principal Investigator

Prof. Michael Zimmermann, MD
Executive Director, ICCIDD Global Network
Head, Human Nutrition Laboratory
Swiss Federal Institute of Technology Zurich
LFV D20, Schmelzbergstr. 7, ETH Zurich 8092 Switzerland
Tel. +41 44 632 8657
Email: michael.zimmermann@hest.ethz.ch

1. Background and objectives

Micronutrient deficiencies are important contributors to the global burden of disease and disability (1). One of the most important micronutrient deficiencies worldwide is iodine deficiency. The WHO estimates that approximately 285 million, or 37% of school-age children and nearly 2 billion individuals worldwide have insufficient iodine intake (2). Iodine deficiency is common, especially in Central and South Asia, where it is estimated that approximately 100 million children are at risk for poor growth due to iodine deficiency (3).

Iodine is a trace element that is an essential component of the thyroid hormones produced by the thyroid gland. Thyroid hormones are essential for normal fetal and child growth and development (4). When dietary iodine requirements are not met, synthesis of the thyroid hormones is impaired. During pregnancy, infancy and childhood, hypothyroidism (low thyroid function) due to iodine deficiency can impair growth and development (5). This results in a number of developmental and functional abnormalities, the spectrum of which is referred to as the Iodine Deficiency Disorders (IDD) (6,7).

There is a well-recognized mechanism to explain the link between iodine deficiency and growth: even small decreases in thyroid hormone action will reduce the effects of growth hormone (either through effects on pituitary secretion or at its receptor) and will also reduce circulating concentrations of insulin-like growth factor (IGF1) and its binding proteins (8). Reduction in the action of growth hormone or the IGF axis due to hypothyroidism will impair somatic growth. Thus, iodine is an essential nutrient for the normal physical growth during gestation and early life.

Salt iodisation has been recommended as a safe, cost-effective and primary strategy to ensure sufficient iodine intake by all individuals, particularly

pregnant women and children (6). Iodised oil may also be an effective intervention in vulnerable groups until iodised salt can be implemented (7).

Why it is important to do this review

A previous systematic review published in 2002 (9) evaluated six intervention trials on the effects of salt iodisation in populations and concluded that iodised salt was an effective means of improving iodine status and found no adverse effects of iodine. However, there was insufficient evidence to make conclusions regarding patient-oriented outcomes, such as growth or cognition. Since that review in 2002, many additional studies have been published which may provide results on these developmental outcomes.

A recent systematic review done in 2011-2012 (not yet published, personal communication, N. Aburto, World Food Program) included only iodised salt studies and included as outcomes all-cause mortality, goiter, cognitive function and cretinism. But it did not examine outcome effects of iodine repletion on growth, either prenatal or postnatal.

Although there is clear evidence of an effect of iodine on growth, **there has never been a systematic review quantifying the effect of correcting iodine deficiency on prenatal and postnatal growth.**

In light of this incomplete evidence, a systematic review of studies investigating the effects on somatic growth of iodised salt and iodised oil in comparison to non-iodised salt or before salt iodisation in the general population is needed.

Particularly because there is an increased emphasis on stunting on the global nutrition agenda, and stunting will likely be a leading post-MDG goal (10,11). Policy leaders in this area often tend to forget that iodine deficiency has adverse effects on growth, and that correction of IDD will be an important contributor to reducing stunting, as part of the multiple intervention package for child health.

Thus, for improved advocacy for iodine deficiency, in order to focus attention and activities and resource allocation to eliminate IDD, we need to do more to establish the evidence base to emphasize the important connection between IDD and stunting.

The results generated from this systematic review will provide the important evidence base for recommendations of iodine and child growth. They will be fundamental to inform the integration of policies and interventions for the prevention of iodine deficiency disorders with those for the prevention of childhood stunting.

Objective

To assess the effects of iodised salt and iodised oil in comparison with placebo or no intervention on growth of the fetus, infant and child, and define the magnitude of the effect on growth of iodine repletion.

2. Protocol of the systematic review

Search methods

We will search The Cochrane CENTRAL, MEDLINE, CNKI, VIP, and Web of Science reference lists. We will search the following web sites' references: Google (www.google.com); the International Council for the Control of Iodine Deficiency Disorders Global Network; Thyroid Disease Manager; and the World Health Organisation. For studies published only in Chinese, a Chinese-speaking study member will hand search the Chinese Journal of Control of Endemic Diseases, the Chinese Journal of Epidemiology, the Chinese Journal of Preventive Medicine, and Studies of Trace Elements and Health. We will also scan the reference lists of papers identified for further trials. For assistance in identifying ongoing or unpublished studies, we will contact the Sprinkles Global Health Initiative, the In-Home Fortification Technical Advisory Group, the nutrition section of the United Nations Children's Fund (UNICEF), the World Food Programme (WFP), the Micronutrient Initiative (MI), the Global Alliance for Improved Nutrition (GAIN), Hellen Keller International (HKI), Sight and Life Foundation, the Department of Nutrition for Health and Development from the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC) and ICCIDD Global Network.

Selection criteria

We will include randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs), quasi-experimental studies, cohort observational studies, and multiple cross-sectional studies with a pre/post study design. All studies must have compared a group of individuals with exposure to iodised salt or iodised oil to a group receiving a placebo, non-iodised salt, or no intervention. We will include monitoring reports of iodisation programs that included a measurement before the introduction of iodised salt to a measurement after the introduction of iodised salt.

Subjects

For postnatal growth, the participants will be children of any age (0-18 years) of either gender. For prenatal growth, the populations will be pregnant women.

Data collection and analysis

Three authors will do the initial data selection and quality assessment of trials independently.

Assessment of risk of bias in included studies

Two reviewers will assess risk of bias and the data will be entered into Review Manager software. We will attempt to contact authors of the original reports for further details if necessary to complete the assessment of risk of bias. We plann to assess risk of bias of all studies by the following quality criteria specified in Cochrane Handbook for Systematic Reviews of Interventions 5.0.2:

- Sequence generation (checking for possible selection bias)
- Allocation concealment (checking for possible selection bias)
- Blinding (checking for possible performance bias)

- Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)
- Selective reporting bias
- Other sources of bias

We will use the same broad categories for assessment of risk of bias in non-randomised studies as in randomised trials, but in addition, we will take into account particular sources of bias associated with different study designs.
Deeks et al. (12) have set out 12 domains for assessing the quality of non-randomised studies: background (e.g. whether the research question was clearly stated); sample definition and selection; interventions (and co-interventions); outcomes; the creation of treatment groups; blinding; soundness of information (e.g. protocol deviations); follow up; analysis (comparability); analysis (outcome); interpretation and presentation and reporting.

A 'risk of bias graph' figure and 'risk of bias summary' figure will be generated. We will assess the impact of individual bias domains on study results at endpoint. GRADEprofiler tool will be used to assess the quality of evidence and to make Summary of Findings tables.

Measures of treatment effect
Continuous variables were expressed as differences in means (MD) with 95% CI. Dichotomous data will be expressed as Risk Ratio (RR) with 95% confidence intervals (CI).

Unit of analysis issues
We will take into account the level at which randomisation occurred, such as cluster-randomised trials and multiple observations for the same outcome.

Dealing with missing data
We will obtain relevant missing data from authors, if feasible and will carefully perform evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT). We will investigate attrition rates, for example drop-outs, losses to follow up and withdrawals and critically appraised issues of missing data.

Assessment of heterogeneity
In the event of substantial clinical or methodological or statistical heterogeneity study results will be reported as meta-analytically pooled effect estimates. We will identify heterogeneity by visual inspection of the forest plots, by using a standard Chi^2 test and a significance level of $\alpha = 0.1$.

We will specifically examine heterogeneity with the I^2 statistic, quantifying inconsistency across studies to assess the impact of heterogeneity on the meta-analysis, where an I^2 statistic of 75% and more will indicate a considerable level of inconsistency (13). When heterogeneity is found, we will attempt to determine the potential causes by examining individual study and subgroup characteristics.

Data synthesis
Data will be summarised statistically if they were available, sufficiently similar and of sufficient quality. We will perform statistical analyses according to the statistical guidelines referenced in the newest version of the Cochrane Handbook for Systematic Reviews of Interventions (13).
When data are reported in various forms that cannot be converted into a standard measures, data will be summarised in a narrative format and in a summary table. For meta-analyses, we will proceed as follows. Data will be included in a meta-analysis if they were of sufficient quality and sufficiently similar. Overall results will be calculated based on the random effects model.

Subgroup analysis and investigation of heterogeneity
We will conduct both overall analysis and subgroup analyses in order to explore effect size differences between groups as follows:

- By iodised salt versus iodised oil
- By concentration of iodine in salt: < 20 ppm versus 20-40 ppm versus > 40 ppm versus unreported/unknown
- By age: prenatal effects (birth weight); infant (0-24 months); preschool child (2-5 years), school age child (6-12 years) and adolescent (13-18 years)
- Estimated baseline iodine status (based on goitre prevalence or urinary iodine excretion level using WHO population cut-off values (6), that is: adequate iodine status, mild iodine deficiency, moderate iodine deficiency, severe iodine deficiency, excess iodine intake.
- By study duration: < = 12 months versus >1 to <= 2 years versus > 2 to <=5 years versus > 5 years.

Sensitivity analysis
We plan to carry out sensitivity analysis to examine the effects of removing studies at high risk of bias from the analysis. We will consider a study to be of high quality if it is graded as adequate in both the randomisation and allocation concealment and in either blinding or loss to follow up.

3. Publication and dissemination

The systematic review will be published in a high-impact peer-reviewed scientific journal with open access. A pdf of the review including a covering abstract will be sent to leading policy and program officers involved in micronutrient programs and child growth.

4. Time plan

The review will be started in January 2013 and completed by September 2013. The results will be published by December 2013.

5. Budget

Item	Budget (USDollars)
Salary for PhD student; 50% Swiss rate @44,000 USD/year	22,000
Search costs, mailings	3,000
Publication costs	1,200
Total	**26,200**

6. References

1. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization, 2009.
2. de Benoist B, McLean E, Andersson M, Rogers L. Iodine deficiency in 2007: global progress since 2003. Food Nutr Bull. 2008;29(3):195-202.
3. Andersson M, Karumbunathan V, Zimmermann MB. Global iodine status in 2011 and trends over the past decade. J Nutr. 2012;142(4):744-50.
4. Larsen PR, Silva JE, Kaplan MM. Relationships between circulating and intracellular thyroid hormones: Physiological and clinical implications. Endocrine Reviews 1981;2:87-102.
5. Zimmermann MB. The effects of iodine deficiency in pregnancy and infancy. Paediatr Perinat Epidemiol 2012;26 suppl 1:108-117..
6. WHO/UNICEF/ICCIDD. Assessment of iodine deficiency disorders and monitoring their elminiation: A guide for programme managers. 3rd edition edition. Geneva: World Health Organization, 2007.
7. Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet. 2008;372(9645):1251-62.
8. Zimmermann MB, Jooste PL, Mabapa NS, Mbhenyane X, Schoeman S, Biebinger R, Chaouki N, Bozo M, Grimci L, Bridson J. Treatment of iodine deficiency in school-age children increases insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations and improves somatic growth. J Clin Endocrinol Metab. 2007;92(2):437-42.
9. Wu T, Liu GJ, Li P, Clar C. Iodised salt for preventing iodine deficiency disorders. Cochrane Database Syst Rev. 2002;(3):CD003204.
10. Ruel MT, Alderman H; Maternal and Child Nutrition Study Group. Nutrition-sensitive interventions and programmes: how can they help to accelerate progress in improving maternal and child nutrition? Lancet. 2013;382(9891):536-51.
11. Stevens GA, Finucane MM, Paciorek CJ, Flaxman SR, White RA, Donner AJ, Ezzati M; Nutrition Impact Model Study Group (Child Growth). Trends in mild, moderate, and severe stunting and underweight, and progress towards MDG 1 in 141 developing countries: a systematic analysis of population representative data. Lancet. 2012;380(9844):824-34.
12. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG, International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group.. Evaluating non-randomised intervention studies.. Health Technol Assess 2003;7(27):1-173.
13. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009] [ ]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.