Effect of salt iodization in pregnancy in preventing neonatal iodine deficiency disorders and adverse pregnancy outcomes in low-and middle- income countries: a systematic review.

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Abstract

Background: Iodine deficiency is a major public health problem throughout the world, particularly for pregnant women and young children. It is the greatest cause of preventable mental retardation in childhood. At present salt iodization is the preferred strategy for control of iodine deficiency disorders and over 120 countries iodize their salts. However, the effects of salt iodization on neonatal iodine deficiency disorders and pregnancy outcomes are not clear. Hence the need to conduct a systematic review to assess the effects of iodized salt in comparison with non-iodized salt on outcomes relating to neonatal iodine deficiency disorders and adverse pregnancy outcomes in pregnant women.

Methods: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Web of Science were searched. Randomized controlled studies, quasi randomized controlled studies and prospective observational studies with a control group with a duration of follow-up of at least nine months were considered for the review. The titles and abstracts of articles retrieved were scanned independently by two groups of two reviewers to assess eligibility, as determined by the inclusion criteria.

Results: The electronic searches have yielded 3792 publications and hand searches revealed two relevant articles. Of these references 576 were duplicates from the electronic searches. After reading the titles and abstracts, six potential studies were retrieved for further assessment. By reading the full article it was found that they do not fulfill the inclusion criteria.

Conclusion: There is currently no sufficient evidence on the role of iodized salt on preventing neonatal iodine deficiency disorders and adverse pregnancy outcomes. Randomized controlled trials are required to evaluate the role of iodized salt in preventing neonatal IDD and adverse pregnancy outcomes.

Key Words: salt iodization, pregnancy, neonatal iodine deficiency disorders, low-and middle-income countries.

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Background

Iodine is an essential trace chemical element required for the production of thyroid hormones, thyroxine (T4) and triiodothyronine (T3) produced by the throid gland (Angermayr and Clar 2004). It is primarily found in oceans as the highly water-soluble iodide ion (Luo *et al.* 2014). It is also found in Kelp (seaweed), sea food, dairy products, certain vegetables and iodized salt (Land *et al.* 2013). In humans, thyroid hormones are important for normal growth and differentiation of cells, fetal growth, nervous system development, bone formation, reproductive tract development (Hulbert 2000) for regulating and stimulating metabolism and temperature control (Larsen 1981).

Iodine deficiency (where the median urinary iodine is below 100 microgram per litre) is a major public health problem throughout the world, particularly for pregnant women and young children. It is the greatest cause of preventable mental retardation in childhood (WHO 2004). Insufficient daily iodine consumption, iodine intake of less than150 microgram(WHO 2007), results in hypothyrodism which causes a range of functional and developmental abnormalities known as "Iodine Deficiency Disorders (IDD)" including: cretinism, goiter, reproductive failures such as abortions and stillbirths, mental retardation, increased susceptibility of the thyroid gland to nuclear radiation, impaired mental function etc (WHO 2004). The most serious effect of IDD is cretinism which occurs in children born to women who are severely deficient in iodine (Sheila 2011). Cretinism has two well known forms: neurological and myxedematous (Zimmermann *et al.* 2008). Neurological cretinism is characterized by severe mental retardation with squint, deaf mutism and motor spasticity while myxedematous cretins show severe growth retardation, incomplete maturation of facial skeleton, puffy features and delayed sexual maturation (Zimmermann 2012). 66-100% or more iodine intake is recommended for pregnant women to produce enough thyroid hormone to meet fetal requirements (Delange 2007).

Iodine deficiency remains one of the most common mincronutrient deficiencies, despite considerable progress globally over the last two and half decades (Sheila 2011). Worldwide about 1.88 billion people and 29.8%, 241 million, of school age children are estimated to have insufficient iodine intakes (Andersson 2012). The main cause of iodine deficiency is a low dietary supply of iodine (Delange 1994). It is common in areas where the soil has low iodine content due to past glaciations or the repeated leaching effects of heavy rainfall and snow. As a result of which crops grown in these areas do not provide adequate amounts of iodine when consumed (WHO 2004). The prevalence of iodine deficiency is highest in the Eastern

Mediterranean region (32%), followed by Africa (20%), Europe (15%) and Southeast Asia (12%) (Ramakrishnan 2002).

The recommended strategy to control iodine deficiency is by increasing iodine intake through supplementation or food fortification (WHO 2004). Though iodine supplementations in the forms of oral solutions and iodized oil were used in the past, the many advantages of iodized salt has restricted use of iodine supplementation for populations living in severely endemic areas with no access to iodized salt (WHO 2004). At present salt iodization is the preferred strategy for control of iodine deficiency disorders and is implemented in over 120 countries(WHO 2004). Though many food vehicles have been fortified with iodine in the past salt is the most commonly used vehicle especially after the World Health Assembly adopted universal salt iodization (USI) as the method of choice to eliminate iodine deficiency (WHO 2004). USI was chosen as the best strategy because of the following reasons: (i) it is widely consumed by virtually all population groups in all countries, with little seasonal variation in consumption patterns, and salt intake is proportional to energy intake/requirements; (ii) in many countries, salt production is limited to a few centres, facilitating quality control; (iii) the technology needed for salt iodization is well established, inexpensive and relatively easy to transfer to countries around the world; (iv) addition of iodate or iodide to salt does not affect the taste or smell of the salt or foods containing iodized salt, and therefore consumer acceptability is high; (v) iodine (mainly from iodate) remains in processed foods that contain salt as a main ingredient, such as bouillon cubes, condiments and powder soups, and hence these products become sources of iodine; and (vi) iodization is inexpensive (the cost of salt iodization per year is estimated at US$ 0.02–0.05 per individual covered, and even less for established salt-iodization programmes). Additionally, the concentration of iodine in salt can easily be adjusted to meet policies aimed at reducing the consumption of salt in order to prevent cardiovascular disease. Many countries have successfully eliminated iodine deficiency disorders or made substantial progress in their control, largely as a result of salt iodization (WHO 2014).

The recent systematic review titled 'Effect and safety of salt iodization to prevent iodine deficiency disorders: a systematic review with meta-analyses' (WHO *et al.* 2014) sponsored by the World Health Organization, included children or the general population in all types of settings (low-, middle-, and high-income countries). In the results of this study no conclusion was made regarding the effects of salt iodization on neonates or pregnancy outcomes. The other systematic review on salt iodization titled 'Iodised salt for preventing iodine deficiency disorders' (Wu *et al.* 2002) was done in 2002 with no conclusions made about improvements on important outcomes such as physical and mental development in children and mortality. Though, the most important damaging disorders induced by iodine deficiency are irreversible mental retardation and cretinism in children which occurs in children born to women who are severely iodine deficient during pregnancy (Sheila 2011), it was not addressed by the above two reviews. Absence of up-to-date systematic reviews on the effects of all forms of iodine supplementation/fortification (including iodized salt) in all of the relevant population groups on relevant growth- and growth-related outcomes has been pointed out by Farebrother et al. (2015). As socio-economic factors are known to affect health outcomes by affecting health behaviors, and clinical care (Swain, 2016), this systematic review focuses on the effect of the most promoted intervention (salt iodization) on neonates and pregnant women in low-and middle- income countries.

Objective

To assess the effects of iodized salt in comparison with non-iodized salt on outcomes relating to neonatal iodine deficiency disorders and adverse pregnancy outcomes in pregnant women.

Methods

Criteria for considering studies for this review

Types of studies

We planned to consider randomized controlled studies, quasi-randomized controlled studies and prospective observational studies with a control group with duration of follow-up of at least nine months.

Types of participants

Pregnant women and neonates in low-and middle-income countries.

Types of interventions

Studies evaluating iodized salt versus control (no treatment or placebo).

Types of outcome measures

Studies that assess any of the following primary and secondary outcomes will be included.

Primary outcomes

- maternal mortality
- neonatal mortality
- low birth weight

- maternal goiter
- neonatal goiter
- "spontaneous abortions"
- abortions
- stillbirths
- preterm births
- cretinism

Secondary outcomes

Maternal and neonatal iodine deficiency as measured by urinary iodine concentration, maternal and neonatal hypothyroidism, adverse effects (iodine-induced hyperthyroidism)

Context: Low-and –middle income countries.

Timing of outcome assessment

Interventions which involved pregnant women for at least 9 months (pregnancy period).

Search methods for identification of studies

Electronic searches: We used the following sources for the identification of studies:

- The Cochrane Central Register of Controlled Trials (CENTRAL) (until February 2017);
- MEDLINE (until February 2017);
- Web of Science (until December 2016)

For detailed search strategy see Appendix 1.

There were no language restrictions when searching for studies.

Searching other resources

Hand searches were also conducted on reference lists of relevant systematic reviews.

Data collection and analysis

Selection of studies

The titles and abstracts of articles retrieved were scanned independently by two groups of two reviewers (MH, YG, DA and FM) to assess eligibility, as determined by the inclusion criteria. Full copies of potentially eligible papers were retrieved. When a title or abstract cannot be rejected with certainty, the full text of the article was obtained for further evaluation. Disagreements at any of the eligibility assessment process were resolved through discussions between the two groups.

Data extraction and management

For studies that fulfilled inclusion criteria, the two groups of two people (MH and YG in one group and DA and FM in the other) were planned to independently extract using standard data extraction forms which include information on study design, study setting, participants (number and characteristics) and provide a full description of the interventions examined with. Details of outcomes measured and results would have been extracted. Data would have been entered into Review Manager (RevMan) software [RevMan 2014] by four review authors (MH, YG, DA, and FM).

Assessing risk of bias in included studies

We planned to use the Cochrane Collaboration's tool for assessing risk of bias to report biases in randomized trials (Higgins and Green 2008) and a Cochrane Risk Of Bias Assessment Tool for non-randomized prospective studies (ACROBAT-NRSi).

Data synthesis

We planned to use a meta-analysis to provide an overall estimate of treatment effect when more than one study examines the same intervention that is when studies use similar methods, and measure the same outcome in similar ways in all populations. When studies do not use similar methods and measure different outcomes, we planned to summarize data in a narrative format. Different comparisons would have been analyzed separately.

Results

Results of the search

The electronic searches have yielded 3792 publications and hand searches revealed two relevant articles. Of these references 576 were duplicates from the electronic searches. After reading the titles and abstracts, six potential studies were retrieved for further assessment. By reading the full article we found that they do not fulfill the inclusion criteria. See Figure 1 for the process summary.

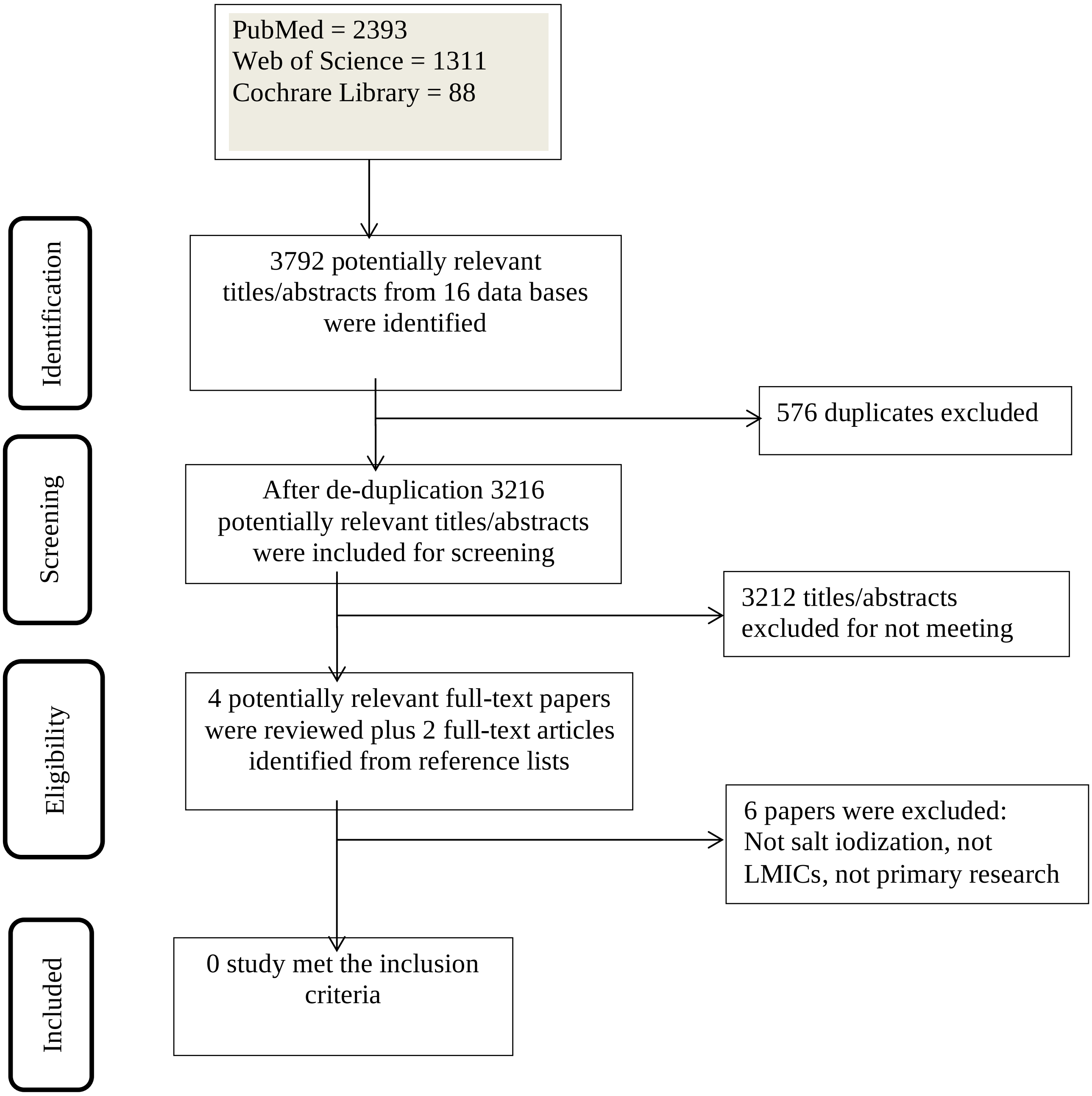

Figure 1: Flow chart of study selection

Description of studies: See table 1 for the characteristics of excluded studies.

Table 1. List of excluded studies and reasons for exclusion

Study	Reason for exclusion
Yan et al. (2005)	Cross sectional study
Mamenko et al. (2013)	A conference abstract; could not tell where it is done
Zimmermann (2007)	Is is a review
Romano et al. (1991)	An RCT conducted in Italy (a high-income country)
Hintz et al. (1988)	An RCT conducted in Germany (a high-income country)
Moleti	A cohort study

Risk of bias in included studies

Not possible

Effect of interventions

Not possible

Data and Analyses

This review has no analyses.

Discussion

There is no evidence from randomized controlled trials, quasi randomized controlled studies and prospective observational studies with a control group on the effect of iodized salt on neonatal IDD and adverse pregnancy outcomes in low- and middle-income countries.

A prospective study evaluating the efficacy of iodine prophylaxis using iodized salt in preventing maternal thyroid failure in pregnant women has shown that long term (for at least two years prior to becoming pregnant) iodized salt consumption has resulted in very low prevalence of maternal thyroid failure compared to a short term consumption (consumption of iodized salt commenced upon becoming pregnant) [Moleti *et al*. 2008]. Another prospective study has shown that iodoprophylaxis using iodized salt prevented increase in thyroid size in pregnant women which might probably help in avoiding maternal and fetal hypothyroidism (Romano *et al*. 1991).

The systematic review by WHO *et al.* (2014) on the effect and safety of salt iodization has included 99 studies, however, no study has addressed IDD on neonates or adverse pregnancy outcomes. The studies were on either the general population or children. Though WHO *et al.* (2014) have concluded that iodized salt has a large effect on reducing the risk cretinism, the conclusion was not supported by RCTs, quasi-experimental or cohort studies. Since, the most important damaging disorders induced by iodine deficiency are irreversible mental retardation and cretinism in children which occurs in children born to women who are severely iodine deficient during pregnancy (Sheila 2011); lack of evidence on this important area should be a big concern to all stake holders.

Implications for practice

There is currently no sufficient evidence on the role of iodized salt on preventing neonatal iodine deficiency disorders and adverse pregnancy outcomes.

Implications for research

Randomized controlled trials, if possible, or quasi-randomized control trials or prospective observational studies are required to evaluate the role of iodized salt in preventing neonatal IDD and adverse pregnancy outcomes in low-and middle-income countries. However, addressing ethical issues of conducting studies on the effect of salt iodization with a control group could be a challenge.

Declarations

Competing interests

None declared

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Authors' contributions

MAMUYE HADIS: drafting of the protocol and review, searching, selection of studies

YOSEF GEBREYOHANNES: searching and selection of studies, drafting of the review

DESALEGN ARARSO: searching and selection of studies

FASIL MENGISTU: searching and selection of studies

AMANUEL DIBABA: drafting of the protocol

ROOS VERSTRAETEN: drafting of the protocol

EDWARD GOKA: drafting protocol and review

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