Iodine supplementation for women during the preconception, pregnancy and postpartum period (Protocol)

De-Regil LM, Harding KB, Peña-Rosas JP, Webster AC

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Iodine supplementation for women during the preconception, pregnancy and postpartum period (Protocol)  
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Iodine supplementation for women during the preconception, pregnancy and postpartum period

Luz Maria De-Regil1, Kimberly B Harding1, Juan Pablo Peña-Rosas2, Angela C Webster3

1Research and Evaluation, Micronutrient Initiative, Ottawa, Canada. 2Evidence and Programme Guidance, Department of Nutrition for Health and Development, World Health Organization, Geneva, Switzerland. 3Sydney School of Public Health, The University of Sydney, Sydney, Australia

Contact address: Luz Maria De-Regil, Research and Evaluation, Micronutrient Initiative, 180 Elgin Street, Suite 1000, Ottawa, ON, K2P 2K3, Canada. lderegil@micronutrient.org.

Editorial group: Cochrane Pregnancy and Childbirth Group.


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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the benefits and harms of supplementation with iodine, alone or in combination with other vitamins and minerals, for women in the preconceptional, pregnancy or postpartum period on their and their children’s outcomes.

BACKGROUND

Description of the condition

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Iodine in preconception, pregnancy and breastfeeding

Throughout pregnancy there are major alterations in thyroid function as a result of metabolic demands and hormonal changes (Glinoer 1997). The concentrations of T4 and T3 rise significantly until approximately mid-gestation and then remain relatively stable until the end of gestation at term. Iodine requirements increase substantially during pregnancy; initially as a result of a 50% increase in thyroid hormone production and a 30% to 50% increase in the renal excretion of iodine (Glinoer 2007a), and later in gestation when iodine passes through the placenta for fetal production of thyroid hormones (Glinoer 1997). Maternal and fetal thyroid hormones are essential in regulating the development of the fetal brain and nervous system including the creation and growth of nerve cells, the formation of synapses, which are required for communication between nerve cells, and myelination which is the formation of a fat-based layer that allows for fast communication.
between nerve cells (Prado 2014). Some of these events begin in the second month of gestation (Prado 2014), so may be influenced by iodine status and thyroid hormone production prior to conception (or prior to knowledge of pregnancy).

During breastfeeding, thyroid hormone production and urinary iodine excretion return to non-pregnancy levels, but iodine requirements remain elevated because iodine is concentrated in the mammary gland for excretion in breastmilk (Leung 2011). Breastmilk iodine content varies with maternal dietary iodine intake and is lowest in iodine-deficient areas and highest where additional iodine is routinely provided through supplements or universal salt iodisation (Azizi 2009). As long as maternal iodine intake is adequate, breastmilk can meet infant iodine needs.

**Recommended iodine intakes**

Minute amounts of iodine are required to meet iodine needs and prevent deficiency. Different agencies have recommended different intakes to meet iodine needs of non-pregnant, pregnant and breastfeeding women, ranging from 150 to 290 µg/day. The International Council for Control of Iodine Deficiency Disorders (ICCIDD), World Health Organization (WHO), and United Nations Children's Fund (UNICEF) recommended a daily iodine intake of 250 µg for pregnant and lactating women (i.e. women breastfeeding their infants) (WHO/UNICEF/ICCIDD 2007). The US Institute of Medicine established a recommended dietary allowance of 220 µg/day for women during pregnancy and 290 µg/day during lactation (IOM 2001). The European Food Safety Authority set the adequate intake among pregnant women and women who are breastfeeding their infants at 200 µg/day (EFSA 2014). All three recommendations suggest 150 µg/day for non-pregnant adult women though recommended intakes for the adolescent period differ.

Both the US Institute of Medicine and the European Commission Scientific Committee on Food have set tolerable upper intake levels for iodine, which are the highest levels of daily intake not likely to pose a risk of adverse health effects in the general population (IOM 2001; SCF 2006). These two organisations’ recommendations vary greatly for non-pregnant, pregnant and breastfeeding women though, with the US Institute of Medicine level at 1100 µg/day and the European Commission level set at 600 µg/day. These levels are not intended for iodine-deficient populations however, as metabolic adaptations to deficiency could result in adverse health effects at lower intakes (Rohner 2014).

**Burden of iodine deficiency**

It is estimated that over 1.8 billion people worldwide have an insufficient iodine intake, putting them at risk of iodine deficiency (Andersson 2012). Europe is the region with the highest proportion of individuals with insufficient intake (44%), whereas South-East Asia has the highest number (540 million). Given the elevated iodine requirements during pregnancy and breastfeeding and the importance of thyroid hormones for growth and development of the nervous system, ensuring adequate status in women and young children is critical. However, as only a limited number of countries have completed surveys in pregnant women and women of reproductive age on national or large sub-national levels, there are insufficient data to directly estimate the regional or global prevalence of low iodine intake in these important target groups (Wong 2011).

**Consequences of iodine deficiency**

The consequences of iodine deficiency, which result from inadequate thyroid hormone production and can affect individuals of any age, sex, and physiological status, are collectively known as iodine deficiency disorders (Hetzel 1983; WHO/UNICEF/ICCIDD 2007). They are most serious and may be irreversible if they occur during pregnancy or early childhood, though the effects depend on the timing and severity of iodine deficiency (Zimmermann 2012a). If the increased iodine requirements during pregnancy are not met, the concentration of T4 diminishes (hypothyroxinaemia) in both mother and fetus, which can lead to irreversible brain damage with intellectual disability and neurologic abnormalities (Glinoer 2007a; Williams 2008). Iodine deficiency in pregnancy has been associated with maternal and fetal goitre and hypothyroidism, increased pregnancy loss and infant mortality, cretinism and intellectual impairments (Dunn 1993; Dunn 2001). Symptoms of hypothyroidism, or an underactive thyroid, include tiredness, weakness, poor memory and difficulty concentrating, weight loss, feeling cold, dry skin and hair loss (Jameson 2005). Globally, iodine deficiency is the most common cause of hypothyroidism (Jameson 2005) and the most common preventable cause of impaired brain development and mental function (WHO/UNICEF 2007).

The effects of iodine deficiency on child development can manifest itself as anything from mild intellectual blunting to full-blown cretinism, with a large proportion of the population suffering intellectual impairment somewhere in between these extremes (Glinoer 2000). Endemic cretinism, the most serious iodine deficiency disorder, is a permanent condition of severely stunted physical and mental development that results from an untreated congenital deficiency of thyroid hormones caused by severe maternal iodine deficiency (Hetzel 1983). It is still unclear whether mild-to-moderate maternal iodine deficiency in humans produces changes in cognitive function. Some evidence suggests that children, with chronic severe iodine deficiency have significant lower intelligence quotient (IQ) scores than those with adequate iodine status (Zimmermann 2009). Some randomised clinical studies conducted in school-age children indicate that cognitive performance may improve with iodine supplementation even in mildly deficient areas (Gordon 2009; Melse-Boonstra 2010). In the absence of iodine these effects are largely preventable by immedi-
ate thyroid hormone replacement, although deficits in memory and IQ may persist over time (Williams 2008). It is also thought that iodine deficiency could be associated with autism (Sullivan 2008) and with children’s attention deficit and hyperactivity disorder (Vermilio 2004).

A variety of factors affect iodine metabolism and thyroid function and can exacerbate iodine deficiency. Other nutritional deficiencies, including of selenium and iron, can lead to decreased thyroid hormone production and cause damage to the thyroid because key enzymes required for thyroid hormone synthesis and metabolism depend on these nutrients (Zimmermann 2002). Iron supplementation has been shown to improve the efficacy of iodine supplementation or salt iodisation in iodine- and iron-deficient children (Hess 2002; Zimmermann 2000).

Compounds found naturally in some foods such as cassava, sorghum, soy and millet, and pollutants in food and water such as perchlorate and nitrate can also negatively affect iodine metabolism and thyroid function (Rohner 2014). Collectively known as goitrogens, these substances can compete with iodine for uptake by the thyroid and impair the activity of key enzymes required to produce thyroid hormones. Infants and young children appear particularly vulnerable to the effects of goitrogens, and effects are generally only seen where there is pre-existing iodine deficiency.

Consequences of excess iodine

Excess iodine exposure can also cause serious negative health effects, and can occur through ingestion of supplements, water or foods with high iodine content or via medical treatments or procedures. Acute iodine poisoning may cause gastrointestinal or cardiovascular symptoms, or even coma, after ingestion of many grams of iodine (Zimmermann 2008). Excess iodine can also cause the thyroid to become over or underactive (hyper or hypothyroidism). Hypothyroidism symptoms are described above. Symptoms of excess thyroid hormone production as a result of hyperthyroidism include hyperactivity, irritability, heat intolerance, palpitations, weakness, fatigue and weight loss (Jameson 2005).

In iodine deficiency, the thyroid is able to adjust to a wide range of iodine intakes, so healthy individuals may tolerate up to 1 mg daily (Zimmermann 2008). In areas of chronic iodine deficiency however, individuals are less tolerant to high iodine intake, especially older adults with longstanding goitre. Iodine-induced hyperthyroidism has been reported in the initial phases of salt iodisation programmes, though it is nearly always temporary (WHO/UNICEF/ICCIDD 2007). It was estimated that 11 countries have excessive iodine intakes (up from seven in 2007) as presented at the Sixty-sixth World Health Assembly in a progress report from the WHO in 2013.

Urinary iodine concentration (UIC)

In conditions of iodine sufficiency, over 90% of ingested iodine is excreted in the urine, whereas in chronic iodine deficiency the excretion may be less than 20%, making urinary iodine concentration (UIC) a good indicator of recent iodine intake, or short-term iodine status (Rohner 2014). UIC has limited utility in assessing individual intake or status because of large variations within and between days (WHO 2013). These variations level out in large population samples though, making UIC a useful population-level indicator. UIC is not a direct indicator of thyroid function, but low values suggest a greater risk of developing thyroid disorders (Rohner 2014).

UIC is commonly collected from school age children and extrapolated to the general population or other population groups; however, neither this group nor non-pregnant women serve as an adequate proxy for pregnant women (Wong 2011). For pregnant women, a median UIC below 150 µg/L is indicative of insufficient iodine intake, 150 to 249 µg/L adequate iodine intake, 250 to 499 µg/L above iodine requirements, and 500 µg/L or higher concentrations suggest an excessive intake (beyond that needed for prevention and control of iodine deficiency) (WHO 2013).

For women who are breastfeeding their infants and children under two years of age, a median UIC of below 100 µg/L indicates insufficient iodine intake, and > 100 µg/L indicates adequate iodine intake. For these population groups, the category of iodine intake is not extrapolated to category of iodine status.

Goitre

The development of goitre, or enlargement of the thyroid gland, begins as an adaptive response when iodine available to the thyroid is not sufficient for adequate thyroid hormone production (Rohner 2014). Goitre responds slowly to changes in iodine intake and is therefore an indicator of longer-term iodine status. In areas of chronic iodine deficiency it can take years for thyroid size to return to normal, and goitre may never completely disappear (Zimmermann 2012).

The presence of goitre can be determined by neck inspection and palpation or by thyroid ultrasonography (Rohner 2014; WHO/UNICEF/ICCIDD 2007). This method however has poor sensitivity and specificity in areas of mild-to-moderate iodine deficiency. In these settings, assessment of thyroid size by ultrasonography is preferred and technology is available for use in field settings. International reference values for thyroid volume using ultrasound are available only for school age children though (Zimmermann 2004).

Thyroid-stimulating hormone (TSH)

This hormone, also known as thyrotropin, is produced by the pituitary gland and stimulates thyroid hormone production and release by the thyroid gland (Rohner 2014). Serum TSH levels
increase in response to low thyroid hormone concentration and decrease in response to high concentration; it is a very sensitive indicator of thyroid function and is the primary screening test for thyroid dysfunction (Jameson 2005). Though TSH levels may rise in response to iodine deficiency, they are often in the normal range, therefore TSH is not considered a sensitive indicator of iodine status (Rohner 2014; Zimmermann 2008). TSH is a useful indicator of iodine nutrition in neonates though because they have high thyroidal iodine turnover (Delange 1998). Moderately elevated levels (higher than 5 mIU/L in whole blood) indicate neonatal iodine deficiency, which is a direct reflection of iodine deficiency during pregnancy (WHO/UNICEF/ICCIDD 2007). A prevalence of less than 3% of infants with moderately elevated TSH is expected in iodine-sufficient regions (WHO/UNICEF/ICCIDD 2007; Rohner 2014). Neonatal TSH screening for congenital hypothyroidism is standard practice in many developed countries (WHO/UNICEF/ICCIDD 2007). This condition, which has genetic causes, is relatively rare (one in 4000 births) and indicated by highly elevated TSH levels (20 mIU/L or higher), requires immediate treatment to prevent permanent neurological damage. Because of a physiological surge in newborns, neonatal TSH assessment must take place at least 48 hours following birth (WHO/UNICEF/ICCIDD 2007). In some countries elevated neonatal TSH may be attributed to the use of beta-iodine-containing antiseptics so results need to be interpreted cautiously in these contexts.

**Thyroid hormones**

Triiodothyronine (T3) and its prohormone, thyroxine (T4), are hormones produced and secreted by the thyroid gland (Rohner 2014). T4 is converted to T3, the active hormone, in peripheral tissues. A very small amount (less than 1%) of T4 and T3 in the blood is not bound to protein, and therefore biologically active. Thyroid hormone assessments typically measure total amounts because the free levels are too low to detect. T3 and T4 levels are direct clinical indicators of thyroid function, but levels are protected in the early stages of thyroid dysfunction and changes occur only at later stages (Rohner 2014). Therefore these thyroid hormones are not good indicators of iodine status, except in cases of severe iodine deficiency. A diagnosis of subclinical hypothyroidism is based on elevated TSH with normal T4 and T3 levels. Overt hypothyroidism occurs when thyroid function further diminishes, as indicated by falling T4 levels, and the diagnosis is based on high TSH and low T4. T3 levels are typically maintained even longer than T4 levels. Some research has shown that neonatal T4 levels are lower in iodine deficient compared to iodine sufficient areas; however, validated norms have not been established for comparison.

**Thyroglobulin (Tg)**

Tg is a protein matrix for thyroid hormone synthesis (Glinoer 1997). Tg levels rise early in pregnancy, and the increase is most pronounced towards the end of gestation. In newborns, Tg levels are normally increased in the first few days, possibly in response to the physiological TSH surge (Pezzino 1981). Tg is an indirect indicator of thyroid function and Tg levels are positively correlated with thyroid volume (Rohner 2014). Tg is elevated in iodine-deficient populations and is also an indirect indicator of iodine status. Levels respond more quickly (weeks to months) to iodine repletion than TSH or goitre (Zimmermann 2008). Assays can be performed on samples collected on dried blood spots and international references ranges are available for school-age children (Zimmermann 2004). The presence of anti-thyroglobulin antibodies, however, complicates interpretation of Tg values (Rohner 2014).

Complex changes in thyroid physiology can make interpretation of thyroid function and iodine status in pregnancy and early infancy difficult, therefore special considerations should be taken into account to avoid misinterpreting results (Laurbøg 2007).

**Description of the intervention**

**Guidance and recommendations**

Since 1993, universal salt iodisation, or the addition of iodine to all salt for human and animal consumption including food industry salt, has been recommended for preventing and controlling iodine deficiency (UNICEF/WHO 1994; WHO 2014). As a result of this long-standing recommendation and the related support for its implementation, most countries have some form of salt iodisation program in place to prevent and control iodine deficiency and its consequences (UNICEF 2008). Universal salt iodisation is widely acknowledged as a cost effective, feasible, and a sustainable approach to control iodine deficiency, and research suggests that successful salt iodisation programmes can meet the needs of population groups susceptible to iodine deficiency and its consequences, specifically pregnant and breastfeeding women and infants (Zimmermann 2007). However, it has been recognised that these groups may need to be targeted with other iodine interventions (Untoro 2007). WHO and UNICEF recommend considering iodine supplementation in pregnant women and women breastfeeding their infants and children from six to 23 months of age, alongside efforts to scale up salt iodisation, in settings where large proportions of the population do not have access to iodised salt (WHO/UNICEF 2007). In addition, where pregnant women are difficult to reach, WHO and UNICEF recommend that supplementation be extended to all women of reproductive age. In some countries, for example the United States, Canada, and Australia, medical bodies have issued specific recommendations for iodine supplementation in women who are pregnant or breast-
feeding (and women considering becoming pregnant in Australia) (ATA 2006; NHMRC 2010).

**Supplement form, dose, and regimen**

**Oral supplements**: several different types of oral iodine supplements are available for public health purposes. These can be broadly divided into frequent low dose (such as daily or weekly), or an infrequent high dose (such as annually or only once). The low-dose formulations usually contain iodine as potassium iodide and come in the form of tablets or drops for oral consumption. Many commercially available multiple-micronutrient supplements including prenatal formulations also contain iodine, often 150 µg for a daily dose (Leung 2009).

High-dose iodine supplements usually come in the form of oral iodised oil capsules; the iodine is stored mainly in the thyroid gland and can meet needs for up to a year. The above-mentioned WHO/UNICEF guidance recommends a single annual dose of 400 mg or a daily dose of 250 µg for pregnant and breastfeeding women (or 150 µg/day for non-pregnant women) (WHO/UNICEF 2007), whereas the United States/Canada and Australian recommendations suggest 150 µg/day (ATA 2006; NHMRC 2010).

**Injectable supplements**: much of the early iodine supplementation research used high-dose intramuscular iodised oil injections (e.g. Pharaoh 1971 and Pretell 1972) and this approach was used in public health programmes especially in the 1970s and 1980s; this would currently be considered a medical intervention that should be provided under medical supervision. Other forms of medical iodine interventions are available including sodium iodide solution used in intravenous parenteral nutrition.

**How the intervention might work**

Iodine requirements increase during pregnancy because of increased thyroid hormone production and iodine excretion, and during breastfeeding because iodine is concentrated in the mammary gland for excretion in breastmilk. If maternal iodine requirements are not met during this period, the production of thyroid hormones may decrease and be inadequate for maternal, fetal and infant needs (Glinoer 2007a). Consequences may include maternal or child hypothyroidism or goitre, pregnancy loss, low birthweight, infant mortality, and developmental delays ranging from mild intellectual impairment to cretinism.

Additional iodine intake through iodine supplementation may help meet the increased iodine needs for thyroid hormone production and transfer to the fetus/infant during pregnancy and the postpartum period and prevent or correct iodine deficiency and its consequences. Iodine supplementation prior to conception could increase iodine stores and thyroid hormone production before the additional demands of pregnancy. This may be especially important in severely iodine-deficient areas to allow time for correction of long-standing deficiency. Even where iodine deficiency is less severe though, additional iodine intake prior to pregnancy may be warranted because thyroid hormones are important for brain and nervous system development events starting as early as the seventh week of gestation (Prado 2014), when women may not know or share with others that they are pregnant.

High-dose iodine supplementation through intramuscular injection prior to, or early in pregnancy has been shown to reduce the incidence of cretinism and improve child cognitive development scores in severely iodine-deficient areas (Bouguema 2013; Zimmermann 2012a). There is also evidence of improved birth-weight, through oral iodine supplementation, and decreased child mortality, through injected iodised oil (Zimmermann 2012a).

From an implementation perspective, pregnant and postpartum women often have contact with the healthcare system, which generally provides or recommends prenatal and sometimes postnatal micronutrient supplementation - usually iron and folic acid. Similarly, iodine supplementation could be integrated into routine antenatal and postnatal care. To reach women prior to pregnancy, existing contacts with the healthcare system or other platforms could be used to provide or recommend iodine supplementation for those planning on becoming pregnant and/or to all women of reproductive age because pregnancies are often unplanned (as is done with folic acid supplementation recommendations in many settings).

**Why it is important to do this review**

It is important to assess the effects and safety of iodine supplementation in women before or during pregnancy and in the postpartum period for optimal maternal and child outcomes and to inform policy making towards the achievement of the WHO global targets for maternal, infant and young child nutrition by 2025 (WHA 2012).

This review will complement the findings of other existing reviews assessing the provision of iodine through a variety of interventions. Mahomed et al conducted one of the first Cochrane reviews on the topic (now withdrawn), examining maternal iodine supplementation in areas of iodine deficiency (Mahomed 2006).

More recently a non-Cochrane review examined the effect of prenatal or periconceptual iodine supplementation on child development, growth and other clinical outcomes (Zhou 2013). The effects of iodine supplementation for preventing iodine deficiency disorders in children (Angermayr 2004) and in preterm infants (Ibrahim 2006) are addressed in other Cochrane reviews. A review on salt iodisation for prevention of iodine deficiency disorders was recently published elsewhere (Aburto 2014) and a Cochrane review on fortification of foods and condiments (other than salt) with iodine for prevention of iodine deficiency disorders (Land 2013) are being conducted. Furthermore, a review on the effect of iodised salt or iodine supplements on prenatal and postnatal growth (Farebrother 2015), and multiple-micronutrient supplementation (Haider 2006) and point-of-use fortification of foods
with multiple micronutrient powders for women during pregnancy (Suchdev 2014) for women during pregnancy are also being reviewed.

**OBJECTIVES**

To assess the benefits and harms of supplementation with iodine, alone or in combination with other vitamins and minerals, for women in the preconceptional, pregnancy or postpartum period on their and their children’s outcomes.

**METHODS**

Criteria for considering studies for this review

**Types of studies**

Will include randomised and quasi-randomised controlled trials with randomisation at either the individual or cluster level. If we identify eligible cross-over trials, we will include only the results from the first period.

**Types of participants**

Women who become pregnant, or pregnant or postpartum women of any chronological age and parity (number of births). We will include studies that randomised women to receive treatment starting at any point prior to conception, during pregnancy or within the first six weeks postpartum. We will exclude studies specifically targeting women diagnosed with severe iodine deficiency or hypothyroidism (as defined by trial authors) or other health problems (e.g. thyroid disease, HIV, tuberculosis).

**Types of interventions**

Oral or injected iodine supplementation (such as tablets, capsules, drops) during preconception, pregnancy or the postpartum period irrespective of compound, dose, frequency or duration. Specifically, we plan to assess the following comparisons:

1. any supplement containing iodine versus same supplement without iodine or no treatment/placebo;
2. any oral iodine supplement versus same supplement without iodine or no treatment/placebo;
3. oral iodine-only supplement versus no intervention or placebo;
4. oral iodine supplement with other vitamins and/or minerals versus only other vitamins and/or minerals (exact same formulation of other vitamins/minerals, but no iodine);
5. any injected iodine supplement versus same supplement without iodine or no treatment/placebo;
6. injected iodine-only supplement versus no intervention or placebo;
7. injected iodine supplement with other vitamins and/or minerals versus only other vitamins and/or minerals (exact same formulation of other vitamins/minerals, but no iodine).

We will include interventions that combine iodine supplementation with co-interventions (e.g. education), only if the co-interventions were the same across study arms. We will exclude studies that examined tube feeding, parenteral nutrition, or food-based interventions (e.g. fortified or biofortified foods, point-of-use fortification with micronutrient powders or lipid-based nutrient supplements).

**Types of outcome measures**

We will include studies which meet the above-mentioned criteria regardless of outcomes reported, though we will only extract the outcomes described below.

**Primary outcomes**

**Maternal**

1. Hypothyroidism (as defined by trial authors).
2. Preterm birth (as defined by trial authors).
3. Any adverse effect (for example iodine-induced hyperthyroidism).

**Infant and children - to 23 months of age**

1. Perinatal mortality (including stillbirth/fetal death and neonatal death, as defined by trial authors).
2. Low birthweight (less than 2500 g).
3. Hypothyroidism (as defined by trial authors).
4. Any adverse effect (for example iodine-induced hyperthyroidism).

**Secondary outcomes**

**Maternal**

1. Spontaneous miscarriage (as defined by trial authors).
2. Thyroid size (assessed by any method).
3. Thyroglobulin (Tg) (µg/L).
4. Insufficient iodine intake (pregnancy: median urinary iodine concentration (UIC) less than 150 µg/L, breastfeeding: median UIC less than 100 µg/L).
5. Excessive iodine intake (pregnancy only: median UIC greater than or equal to 500 µg/L).
Infant and children - to 23 months of age
1. Small for gestational age (as defined by trial authors).
2. Congenital anomalies (including cretinism, as defined by trial authors).
4. Thyroid size (assessed by any method).
5. Insufficient iodine intake (median UIC less than 100 µg/L).
6. Mental or motor development (as defined by trial authors).

For relevant maternal outcomes, we will include both the pregnancy and postpartum period. If maternal outcomes are assessed at multiple time points, unless otherwise specified, we will use the last assessment during pregnancy and the last assessment in the postpartum period, or the last assessment during the intervention period and the last assessment during the follow-up period. We will not include any outcomes during the preconception period.

For infant and child outcomes assessed at multiple time points, where relevant we will include the neonatal period (to 28 days), infancy (under one year), and childhood (beyond one year). We will summarise primary outcomes in 'Summary of findings' tables.

Urinary and breastmilk iodine concentrations are probably the most common indicators of iodine status; they provide important information on the adherence and biological response to the intervention or potential contamination in the control group. However these indicators are generally highly skewed and are typically reported as median with some description of the range. As we may not have access to primary data, we plan to present these outcomes in a table in the Appendix but they will not be included in a meta-analysis and will not directly inform the conclusions of the review.

Search methods for identification of studies
The following methods section is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches
We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group’s Trials Register. The Cochrane Pregnancy and Childbirth Group’s Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (OVID);
3. weekly searches of Embase (OVID);
4. monthly searches of CINAHL (Ebsco);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Data collection and analysis
The following methods section is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies
Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person. We will include studies published as abstracts but if we cannot assess quality and extract information (after attempting to contact authors), these studies will be marked as “awaiting classification”.

We will create a ‘Study flow’ diagram to map out the number of records identified, included and excluded, as well as reasons for exclusion.
Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2014) and check them for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data are less than 20% and are balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ‘as treated’ analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias (e.g. level of missing data is unclear).

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study’s pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study’s pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
• unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:
• low risk of other bias;
• high risk of other bias;
• unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Assessing the quality of the evidence using GRADE

We will assess the overall quality of the evidence for primary outcomes using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the primary outcomes for comparison number 1. GRADE profiler (GRADEpro 2014) will be used to import data from Review Manager (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the Handbook using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

If we identify any cross-over trials otherwise eligible for inclusion, we will include them but use only data from the first period (if the data are presented in this way), therefore, additional methods for 'Risk of bias' assessment and analysis are not needed.

Other unit of analysis issues

For studies with more than two intervention groups (multi-arm studies e.g. using different doses), we will only include directly relevant arms. If we identify studies with more than one relevant arm we will combine the arms into a single pair-wise comparison (Higgins 2011) and include the disaggregated data in the corresponding subgroup category. To avoid double counting participants, if the control group is shared by different study arms, we will divide the control group (events and total population) over the number of relevant subgroup categories. For studies that included non-pregnant women, we will only include those who became pregnant. If a study also examined supplementing both the mother and infant, and was otherwise eligible, we will include that study arm and the maternal data but exclude the infant data.
We will include all relevant details in the 'Characteristics of included studies' tables.

**Dealing with missing data**
For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

**Assessment of heterogeneity**
We will assess statistical heterogeneity in each meta-analysis using the Tau², P² and Chi² statistics. We will regard heterogeneity as substantial if an P is greater than 30% and either the Tau² is greater than zero, or there is a low P value (less than 0.10) in the Chi² test for heterogeneity. If we identify substantial heterogeneity (above 30%), we plan to explore it by pre-specified subgroup analysis.

**Assessment of reporting biases**
If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

**Data synthesis**
We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials’ populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau² and P².

**Subgroup analysis and investigation of heterogeneity**
If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful and, if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses, when information is available. We will use only information reported by the trial, unless otherwise specified.

1. By period of supplementation: only before pregnancy versus only during pregnancy versus only during the postpartum period versus mixed.
2. By supplementation regimen: daily versus weekly versus annual.
3. By access to iodised salt: less than 50% versus 50% to 69% versus greater than or equal to 70% versus not reported.
4. By iodine status of the participants at the start of the intervention: adequate versus mild or moderate deficiency versus severe deficiency versus unknown (as defined by trial authors, or following WHO-recommended criteria).
5. By breastfeeding status: yes at any time versus never versus mixed/not reported. Note: this factor in not related to pregnancy outcomes therefore this analysis will be performed only on maternal postpartum and child outcomes.

We will include only the primary outcomes in subgroup analyses. If we find substantial heterogeneity for any primary outcome, we will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test P² value.

**Sensitivity analysis**
We will conduct sensitivity analysis based on the risk of bias of the studies. We will consider a study to be of high quality if it is graded as “low risk of bias” in both randomisation and allocation concealment and in either blinding or loss to follow-up. Other sensitivity analyses may be performed depending on the studies included, for example, if we identify and include any cluster trials we will carry out sensitivity analysis using a range of ICC values. We will carry out sensitivity analysis for primary outcomes only.

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The World Health Organization (and Luz Maria De-Regil, Kimberly Harding and Angela C Webster) retains copyright and all other rights in the manuscript of this protocol as submitted for publication, including any revisions or updates to the manuscript which WHO may make from time to time.

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Zimmermann 2008
APPENDICES

Appendix 1. Search strategy and terms

Iodine AND pregnancy
iodine AND pregnant
Iodine AND postnatal
Iodine AND postpartum
iodine AND breastfeeding
Iodine and lactation

These are suggested terms and the full search methods will be documented in the review.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of this protocol.

Disclaimer: Juan Pablo Peña-Rosas is currently a staff member of the World Health Organization (WHO). Luz Maria De-Regil and Kimberly Harding are employed full-time by the Micronutrient Initiative (MI). The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of WHO or MI.

DECLARATIONS OF INTEREST

Luz Maria De-Regil is employed by the Micronutrient Initiative (MI), an international not-for-profit organisation that implements salt fortification programmes, to ensure populations have adequate iodine levels. As an employee of MI she will not assess any study sponsored by MI that could potentially meet the inclusion criteria of this review. She is also a board member for the Iodine Global Network.

Kimberly Harding is employed by the Micronutrient Initiative (MI), an international not-for-profit organisation that implements salt fortification programmes, to ensure populations have adequate iodine levels. As an employee of MI she will not assess any study sponsored by MI that could potentially meet the inclusion criteria of this review.

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