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[Intervention Review]

# Iodine supplementation for women during the preconception, pregnancy and postpartum period

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## ABSTRACT

### Background

Iodine is an essential nutrient required for the biosynthesis of thyroid hormones, which are responsible for regulating growth, development and metabolism. Iodine requirements increase substantially during pregnancy and breastfeeding. If requirements are not met during these periods, the production of thyroid hormones may decrease and be inadequate for maternal, fetal and infant needs. The provision of iodine supplements may help meet the increased iodine needs during pregnancy and the postpartum period and prevent or correct iodine deficiency and its consequences.

### 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.

### Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (14 November 2016), and the WHO International Clinical Trials Registry Platform (ICTRP) (17 November 2016), contacted experts in the field and searched the reference lists of retrieved studies and other relevant papers.

### Selection criteria

Randomized and quasi-randomized controlled trials with randomisation at either the individual or cluster level comparing injected or oral iodine supplementation (such as tablets, capsules, drops) during preconception, pregnancy or the postpartum period irrespective of iodine compound, dose, frequency or duration.

## Data collection and analysis

Two review authors independently assessed trial eligibility, risk of bias, extracted data and conducted checks for accuracy. We used the GRADE approach to assess the quality of the evidence for primary outcomes.

We anticipated high heterogeneity among trials, and we pooled trial results using random-effects models and were cautious in our interpretation of the pooled results.

## Main results

We included 14 studies and excluded 48 studies. We identified five ongoing or unpublished studies and two studies are awaiting classification. Eleven trials involving over 2700 women contributed data for the comparisons in this review (in three trials, the primary or secondary outcomes were not reported).

### Maternal primary outcomes

Iodine supplementation decreased the likelihood of the adverse effect of postpartum hyperthyroidism by 68% (average risk ratio (RR) 0.32; 95% confidence interval (CI) 0.11 to 0.91, three trials in mild to moderate iodine deficiency settings, 543 women, no statistical heterogeneity, low-quality evidence) and increased the likelihood of the adverse effect of digestive intolerance in pregnancy by 15 times (average RR 15.33; 95% CI 2.07 to 113.70, one trial in a mild-deficiency setting, 76 women, very low-quality evidence).

There were no clear differences between groups for hypothyroidism in pregnancy or postpartum (pregnancy: average RR 1.90; 95% CI 0.57 to 6.38, one trial, 365 women, low-quality evidence, and postpartum: average RR 0.44; 95% CI 0.06 to 3.42, three trials, 540 women, no statistical heterogeneity, low-quality evidence), preterm birth (average RR 0.71; 95% CI 0.30 to 1.66, two trials, 376 women, statistical heterogeneity, low-quality evidence) or the maternal adverse effects of elevated thyroid peroxidase antibodies (TPO-ab) in pregnancy or postpartum (average RR 0.95; 95% CI 0.44 to 2.07, one trial, 359 women, low-quality evidence, average RR 1.01; 95% CI 0.78 to 1.30, three trials, 397 women, no statistical heterogeneity, low-quality evidence), or hyperthyroidism in pregnancy (average RR 1.90; 95% CI 0.57 to 6.38, one trial, 365 women, low-quality evidence). All of the trials contributing data to these outcomes took place in settings with mild to moderate iodine deficiency.

### Infant/child primary outcomes

Compared with those who did not receive iodine, those who received iodine supplements had a 34% lower likelihood of perinatal mortality, however this difference was not statistically significant (average RR 0.66; 95% CI 0.42 to 1.03, two trials, 457 assessments, low-quality evidence). All of the perinatal deaths occurred in one trial conducted in a severely iodine-deficient setting. There were no clear differences between groups for low birthweight (average RR 0.56; 95% CI 0.26 to 1.23, two trials, 377 infants, no statistical heterogeneity, low-quality evidence), neonatal hypothyroidism/elevated thyroid-stimulating hormone (TSH) (average RR 0.58; 95% CI 0.11 to 3.12, two trials, 260 infants, very low-quality evidence) or the adverse effect of elevated neonatal thyroid peroxidase antibodies (TPO-ab) (average RR 0.61; 95% CI 0.07 to 5.70, one trial, 108 infants, very low-quality evidence). All of the trials contributing data to these outcomes took place in areas with mild to moderate iodine deficiency. No trials reported on hypothyroidism/elevated TSH or any adverse effect beyond the neonatal period.

## Authors' conclusions

There were insufficient data to reach any meaningful conclusions on the benefits and harms of routine iodine supplementation in women before, during or after pregnancy. The available evidence suggested that iodine supplementation decreases the likelihood of postpartum hyperthyroidism and increases the likelihood of the adverse effect of digestive intolerance in pregnancy - both considered potential adverse effects. We considered evidence for these outcomes low or very low quality, however, because of study design limitations and wide confidence intervals. In addition, due to the small number of trials and included women in our meta-analyses, these findings must be interpreted with caution. There were no clear effects on other important maternal or child outcomes though these findings must also be interpreted cautiously due to limited data and low-quality trials. Additionally, almost all of the evidence came from settings with mild or moderate iodine deficiency and therefore may not be applicable to settings with severe deficiency.

More high-quality randomised controlled trials are needed on iodine supplementation before, during and after pregnancy on maternal and infant/child outcomes. However, it may be unethical to compare iodine to placebo or no treatment in severe deficiency settings. Trials may also be unfeasible in settings where pregnant and lactating women commonly take prenatal supplements with iodine. Information is needed on optimal timing of initiation as well as supplementation regimen and dose. Future trials should consider the outcomes in this review and follow children beyond the neonatal period. Future trials should employ adequate sample sizes, assess

potential adverse effects (including the nature and extent of digestive intolerance), and be reported in a way that allows assessment of risk of bias, full data extraction and analysis by the subgroups specified in this review.

## **PLAIN LANGUAGE SUMMARY**

### **Iodine supplementation for women before, during or after pregnancy**

#### **What is the issue?**

It is estimated that over 1.8 billion people worldwide do not get enough iodine in their diet, putting them at risk of iodine deficiency. Iodine is an essential nutrient needed in small amounts for the body to make thyroid hormones. The World Health Organization (WHO) recommends that iodine is added to salt to prevent problems caused by lack of iodine. Women who are pregnant or breastfeeding need extra iodine, which puts them at greater risk of deficiency. The breast milk contains iodine for the infant.

#### **Why is this important?**

Thyroid function is increased during pregnancy as thyroid hormones produced by the mother (and the baby as the pregnancy progresses) are essential for growth and development of the baby and to regulate the development of the brain and nervous system. Nervous tissue begins to develop as early as the second month of pregnancy. If women have too little iodine during pregnancy or infants have too little during early childhood, the damage may be irreversible. Research has shown that severe iodine deficiency can stunt children's normal physical growth as well as harm normal mental development, resulting in lower intelligence quotients. Less is known about the consequences of mild or moderate deficiency. Too much iodine can also cause harm and have negative effects on mothers and babies, for example by causing the thyroid to become overactive.

Although salt is the commonly the main source of iodine, expert medical groups recommend that women in many countries take iodine supplements during and following pregnancy to help ensure their iodine needs are met.

#### **What evidence did we find?**

We searched for evidence in November 2016 and identified 14 randomised controlled trials of iodine supplements in the form of tablets, capsules, drops or injections before, during or after pregnancy. Eleven trials with over 2700 women contributed findings to the review. Eight trials compared iodine with no treatment or a placebo and three trials compared iodine given with other vitamins and minerals against only the vitamins and minerals.

Women who received iodine supplements were less likely to develop the unwanted effect of hyperthyroidism (an overactive thyroid gland) after giving birth (three trials involving 543 women) but they were more likely to experience nausea or vomiting during pregnancy (one trial involving 76 women) when compared to those who did not receive iodine. One trial (365 women) did not find any difference in the number of women with an overactive thyroid gland during pregnancy. The number of women with an underactive thyroid gland (hypothyroidism) was not clearly different either during pregnancy (one trial involving 365 women) or after giving birth (three trials involving 540 women) when iodine supplements were given. A similar number of women had raised thyroid antibodies during pregnancy (one trial, 359 women) and after giving birth (three trials, 397 women). We found no clear differences between women given iodine supplements and those not when looking at preterm births (two trials, 376 women) or deaths around the time of giving birth (two trials, 457 women), babies born with a low birthweight (two trials, 377 babies), newborn babies with an underactive thyroid gland (two trials, 260 babies) or with raised thyroid antibodies (one trial, 108 babies).

The quality of the evidence was low to very low, mostly because few trials looked at each outcome or because of limitations in the study designs. Most of the findings were from one or two trials and small numbers of women were included. This means we are not confident in the results.

#### **What does this mean?**

The potential benefits and harms of any intervention must be weighed as part of deciding whether to use it. Our Cochrane Review provides a summary of the evidence but there were not enough data for any meaningful conclusions on the benefits and harms of routine iodine supplementation in women before, during or after pregnancy. The limited information we found suggests there are benefits and risks of iodine supplementation. More research will clarify the effects and safety of this intervention. Future research should use randomised controlled trial designs where practical and ethical, and include the outcomes from this review.