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Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

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ABSTRACT

Background

Over the last decade there has been enhanced awareness of the appreciable morbidity of thyroid dysfunction, particularly thyroid deficiency. Since treating clinical and subclinical hypothyroidism may reduce adverse obstetric outcomes, it is crucial to identify which interventions are safe and effective.

Objectives

To identify interventions used in the management of hypothyroidism and subclinical hypothyroidism pre-pregnancy or during pregnancy and to ascertain the impact of these interventions on important maternal, fetal, neonatal and childhood outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 March 2013).

Selection criteria

Randomised controlled trials (RCTs) and quasi-randomised controlled trials that compared a pharmacological intervention for hypothyroidism and subclinical hypothyroidism pre-pregnancy or during pregnancy with another intervention or placebo.

Data collection and analysis

Two review authors assessed trial eligibility and quality and extracted the data.

Main results

We included four RCTs of moderate risk of bias involving 362 women. In one trial of 115 women, levothyroxine therapy to treat pregnant euthyroid (normal thyroid function) women with thyroid peroxidase antibodies was not shown to reduce pre-eclampsia significantly (risk ratio (RR) 0.61; 95% confidence interval (CI) 0.11 to 3.48) but did significantly reduce preterm birth by 72% (RR 0.28; 95% CI 0.10 to 0.80). Two trials of 30 and 48 hypothyroid women respectively compared levothyroxine doses, but both trials...
reported only biochemical outcomes. A trial of 169 women compared the trace element selenomethionine (selenium) with placebo and no significant differences were seen for either pre-eclampsia (RR 1.44; 95% CI 0.25 to 8.38) or preterm birth (RR 0.96; 95% CI 0.20 to 4.61). None of the four trials reported on childhood neurodevelopmental delay.

There was a non-significant trend towards fewer miscarriages with levothyroxine, and selenium showed some favourable impact on postpartum thyroid function and a decreased incidence of moderate to advanced postpartum thyroiditis.

Authors' conclusions

This review found no difference between levothyroxine therapy and a control for treating pregnant euthyroid women with thyroid peroxidase antibodies for the outcome of pre-eclampsia, however a reduction in preterm birth and a trend towards reduced miscarriage with levothyroxine was shown. This review also showed no difference for pre-eclampsia or preterm birth when selenium was compared with placebo, however a promising reduction in postpartum thyroiditis was shown. Childhood neurodevelopmental delay was not assessed by any trial included in the review.

Given that this review is based on four trials of moderate risk of bias, with only two trials contributing data (n = 284), there is insufficient evidence to recommend the use of one intervention for clinical or subclinical hypothyroidism pre-pregnancy or during pregnancy over another, for improving maternal, fetal, neonatal and childhood outcomes.

PLAIN LANGUAGE SUMMARY

Interventions to reduce harm to women and their children from untreated low levels of thyroid hormone in pregnancy

The thyroid is a butterfly-shaped gland at the front of the oesophagus/throat that produces thyroid hormone. Thyroid hormone helps the body to make energy, keeps body temperature regulated and assists other organs in their functions. Hypothyroidism (a deficiency of thyroid hormone) is a relatively common illness that can cause fatigue, constipation, muscle cramps and weakness, hair loss, dry skin, intolerance to cold, depression and weight gain. Medication is with levothyroxine. Selenium is a trace element that changes the expression of selenoproteins. These act as antioxidants and appear to decrease thyroid inflammation in autoimmune thyroiditis. Pregnant women with subclinical hypothyroidism have abnormal thyroid hormone levels but no symptoms. They are at a increased risk of miscarriage, pre-eclampsia and preterm birth with impaired neuropsychological development in the child.

We identified four randomised studies involving only 362 women with hypothyroidism. In one trial of 115 women with thyroid autoantibodies but normal thyroid hormone levels, levothyroxine clearly reduced the risk of preterm birth by 72% compared with no treatment. The risk of women developing pre-eclampsia was not reduced, but there was a trend toward a reduction in miscarriage. In a study of 169 women with autoimmune hypothyroidism, supplementation with selenium did not decrease preterm birth rates or pre-eclampsia, but appeared to reduce moderate to severe inflammation of the thyroid gland and thyroid dysfunction after the birth. The third and fourth studies looked at different doses of levothyroxine on thyroid hormone levels.

Levothyroxine is an established treatment for women with symptomatic hypothyroidism, but it may also benefit women with low thyroid levels who do not have symptoms. Selenium also shows promise for women with hypothyroidism but needs further testing.

BACKGROUND

Description of the condition

Thyroid disease is the second most common endocrine disorder (after diabetes mellitus) affecting women of reproductive age. The incidence of hypothyroidism during pregnancy is estimated to be 0.3% to 0.5% for overt hypothyroidism and 3% to 5% for subclinical hypothyroidism (Abalovich 2007; Casey 2006; Casey 2007). Overt hypothyroidism is defined as symptomatic thyroid hormone deficiency (low free thyroxine hormone, elevated thyroid stimulating hormone (TSH)), whilst subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency (normal free thyroxine but elevated TSH), in women with few or no clinical
features (Jameson 2008). Isolated maternal hypothyroxinaemia is defined as low free thyroxine concentrations with a normal range TSH (Casey 2007). Thyroid hormone helps the body to make energy, keeps body temperature regulated and assist other organs in their functions. Symptoms of hypothyroidism include weight gain, constipation, fatigue, muscle cramps and weakness, intolerance of cold weather and dry skin.

**Thyroid dysfunction in pregnancy**

Over the last decade there has been enhanced awareness of the appreciable morbidity of thyroid dysfunction, particularly thyroid deficiency (Abalovich 2007; Casey 2007; Lazarus 2005). Whilst the association between maternal hypothyroidism and increased perinatal morbidity and mortality has been described for over a century, prospective cohort studies have drawn substantial attention to the problem (Haddow 1999; Pop 1999). The increasing evidence for impaired neuropsychological development in the children of women with variously defined hypothyroidism has fuelled a resurgence of interest. In 2007, an international task force was created to develop evidence-based guidelines for management of thyroid dysfunction (Gharib 2005), with some recommending thyroxine replacement for subclinically hypothyroid women, arguably without a great deal of evidence (Casey 2007).

**Causes of hypothyroidism in pregnancy**

Worldwide, particularly in mountainous regions and in central Africa, South America and northern Asia, the most common cause of hypothyroidism is iodine deficiency (Jameson 2008). Iodine is a trace element and is essential for the formation of thyroid hormone (T4) and triiodothyronine (T3). The World Health Organization (WHO) estimates that about two billion people are iodine deficient (urinary iodine excretion less than 100 micrograms (µg) per day). In areas of iodine sufficiency, the most common cause of hypothyroidism in pregnant women is Hashimoto’s disease (chronic thyroiditis), an autoimmune disease where the body’s own antibodies attack the thyroid. The mean annual incidence rate is up to four per thousand women, perhaps higher in certain populations, such as the Japanese, where genetic factors and a high-iodine diet may contribute to an increased incidence. Detection of thyroid autoantibodies (to thyroid peroxidase or thyroglobulin) confirms the autoimmune origin.

Autoantibodies are proteins created by the body in response to the individual’s self antigens, i.e. normal endogenous tissues. There are two main autoantibodies that may damage the thyroid leading to hypothyroidism - thyroid peroxidase autoantibody and thyroglobulin antibody. Antithyroid antibodies are surprisingly prevalent in pregnancy, found in approximately 10% of women in the second trimester (Lazarus 2005). A recent Australian study has found that 18% of women in the late first trimester had antithyroid antibodies (against either thyroperoxidase or thyroglobulin), which are associated with subtle effects on thyroid function (McElduff 2008). Women with antithyroid antibodies have an increased risk of infertility, miscarriage, preterm birth, postpartum depression and postpartum thyroiditis, even in the absence of obvious thyroid dysfunction (Abalovich 2007; Lazarus 2005; Negro 2006). While the mechanisms underlying this association are unclear, correcting mild subclinical hypothyroidism early in pregnancy or even pre-conception may reduce miscarriage rates.

Thyroidectomy or ablative radiiodine therapies are other important primary causes of hypothyroidism in the developed world. Secondary hypothyroidism is pituitary in origin; for example, irradiation, hypophysectomy (surgical removal of the pituitary gland), or Sheehan’s syndrome (postpartum pituitary necrosis). Tertiary (hypothalamic) hypothyroidism is rare.

**Adverse effects on pregnancy**

Both overt and subclinical hypothyroidism have significant adverse effects on pregnancy and fetal development, more frequently seen in symptomatic women. Firstly, as untreated hypothyroidism is associated with anovulatory cycles there is often difficulty with conception. When pregnancy occurs there is an increased incidence of miscarriage, pregnancy-induced hypertension and its more severe form pre-eclampsia, as well as placental abruption, anaemia and postpartum haemorrhage as reported in several retrospective cohorts (Casey 2006; Casey 2007; Davis 1988; Harborne 2004; Leung 1993). The strong association between inadequately treated hypothyroidism and pre-eclampsia is not surprising given that hypothyroidism is an accepted cause of reversible hypertension in the non-pregnant population. The obstetric complications of hypothyroidism contribute to the overall increase in frequency of adverse neonatal outcomes, which include preterm birth, low birthweight, increased admission to neonatal intensive care and increased perinatal morbidity and mortality.

**Adverse effects on fetal neurodevelopment**

The harmful impact of maternal hypothyroidism on the developing fetal brain has been appreciated for decades. Congenital cretinism is a well documented syndrome of growth restriction, deafness and neuropsychological impairment, resulting from severe iodine deficiency or untreated congenital hypothyroidism (Cao 1994).

In 1969, it was reported that ‘mild’ maternal hypothyroidism alone was associated with lower IQ levels in the offspring (Man 1969). This susceptibility of the fetal brain to mild or subclinical hypothyroidism was further demonstrated by a prospective American study of children born to 62 women with thyrotropin concentrations at or above the 98th percentile (Haddow 1999). Of
these children, 15% had scores of 85 or less on the Weschler Intelligence Scale (85 is on the 16th centile), compared with 5% of children of matched control women. In the same year, a prospective study identified a cohort of 220 asymptomatic women at 12 weeks' gestation with free thyroxine concentrations below the tenth centile (Pop 1999). Their children were found to have significant developmental delay at 10 months and two years as measured by the Bayley Scales of Infant Development (risk ratio 5.8, 95% confidence interval 1.3 to 12.6). The Bayley Scales of Infant Development are recognised internationally as one of the most comprehensive tools in the assessment of motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers, ages nought to three. The children perform a series of developmental play tasks and in the study above, they were compared with children of mothers with higher free thyroxine concentrations. It was concluded that prior to 12 weeks when the fetal thyroid begins to concentrate iodine, normal brain development is reliant upon adequate maternal thyroid hormone.

In contrast, a more recent prospective study of 10,990 women in America and Ireland with biochemical evidence of subclinical hypothyroidism and isolated maternal hypothyroxinaemia found no excessive adverse pregnancy outcomes compared with matched controls (Cleary-Goldman 2006). The biological significance of isolated maternal hypothyroxinaemia has been questioned however. No adverse perinatal outcomes were reported from a retrospective case review of 17,000 women with an incidence of isolated hypothyroxinaemia of 1.3% (Casey 2007). It was suggested by Casey and colleagues that any significant poor outcomes from the Cleary-Goldman study were likely diluted by the inclusion of women with isolated maternal hypothyroxinaemia. The International Endocrine Society conclude that overt hypothyroidism is associated with damage to fetal intellectual development. Whether subclinical dysfunction carries this risk remains to be seen, but treatment of both conditions is nonetheless advised (Abalovich 2007).

Description of the intervention

Davis 1988 stated "it is interesting to speculate what salutary effect T4 supplementation might have in improving pregnancy outcome". Since this time it has been well documented that appropriate thyroxine replacement may decrease the risk of adverse pregnancy outcomes. Treating maternal hypothyroidism also appears beneficial for the child. By systematically identifying and adequately treating women with overt and subclinical hypothyroidism, there is a significant reduction in childhood neurodevelopmental morbidity (Abalovich 2002; Negro 2006). As the symptoms of hypothyroidism are non-specific, a heightened suspicion for investigation is imperative. Symptoms like cold intolerance and bradycardia are more specific, but many such as constipation, weight gain and fatigue may be physiological in pregnancy. If these symptoms predate the pregnancy, however, or are particularly persistent or troublesome, testing of thyroid function is warranted. Iodine is an important intervention in preventing adverse outcomes of maternal hypothyroidism. Iodine deficiency is the main cause for potentially preventable mental retardation in childhood, known as cretinism (Angermayr 2004). Iodised salt, bread, water, oil and iodine tablets are commonly used for preventing iodine deficiency disorders. This subject is the topic of two other Cochrane reviews, entitled 'Iodine supplementation for preventing iodine-deficiency disorders in children' (Angermayr 2004) and 'Iodised salt for preventing iodine-deficiency disorders' (Wu 2002).

How the intervention might work

In iodine-sufficient populations, replacement with thyroxine to normalise TSH concentrations, is a well-known intervention for hypothyroidism. The literature suggests an increased thyroxine requirement for hypothyroid women in pregnancy, on average 30% to 50% above pregnancy dosage (Harborne 2004). There are several biological explanations including increased metabolism of thyroxine, the increased distribution volume of thyroid hormones and the rise in thyroid binding globulin (TBG) concentrations. The timing of the increase in thyroxine requirement during pregnancy is still controversial. It has been suggested that the non-pregnant total thyroxine range (5 to 12 μg/dL) should be increased after the first trimester by multiplying the range by 1.5-fold (Abalovich 2007). The classical reference range for thyrotrpin (thyroid stimulating hormone (TSH)) is 0.4 to 4 mIU/L, but human chorionic gonadotrophin may lead to lower concentrations. There is a paucity of good quality evidence regarding the normal upper and lower limits for serum TSH and free T4 concentrations in pregnancy. There are suggested clinical practice guidelines regarding the initial treatment dose, the frequency of dose adjustments and the intensity of thyroid function monitoring, but no consensus has been reached (Abalovich 2007). There is insufficient evidence in regards to the efficacy and safety of various thyroxine dose adjustments. Recently the trace element selenium has been shown during pregnancy and postpartum to reduce the incidence of hypothyroidism (Negro 2007). Selenium modifies the expression of selenoproteins, which act as antioxidants and appear to decrease thyroid inflammatory activity in autoimmune thyroiditis. In women with thyroid peroxidase antibodies, there is a high incidence of permanent hypothyroidism following postpartum thyroid dysfunction, up to 30%, as described by Premawardhana 2000. Prevention would be of obvious benefit to women of reproductive age.

Why it is important to do this review

This review updates a previously published Cochrane review on treatment interventions for hypothyroidism and subclinical hy-
pothyroidism pre-pregnancy and during pregnancy (Reid 2010).
This review found some promising evidence to support the use of levothyroxine in autoimmune and subclinical hypothyroidism, with a reduction in preterm birth observed, and revealed selenomethionine to be a promising intervention in women with thyroid autoantibodies in relation to a reduction in postpartum thyroiditis. The review concluded however, that high-quality evidence from randomised trials was lacking in this area.
The Endocrine Society Clinical Practice Guidelines (Abalovich 2007) currently conclude that there is “probable benefit” to treatment and a probable low incidence of adverse outcomes from intervention. In thyroid-deficient women of reproductive age, the rationale for treatment is to relieve symptoms, reduce adverse obstetric and neonatal outcomes and to maintain normal growth and intellectual development in the offspring. Well-controlled hypothyroidism does not usually pose major problems in pregnancy and there may be good evidence that the benefits of appropriate interventions largely outweigh the potential risks associated with treatment.
There is clearly documented evidence of the strong association between thyroid deficiency in pregnancy and major adverse outcomes for the mother and developing fetus. It should be remembered that some of these women have iatrogenic hypothyroidism secondary to treatment of hyperthyroidism and that the fetus may be exposed to thyroid autoantibodies. The potential screening test (TSH) is easily accessible, reliable (in conjunction with the clinical context) and inexpensive. The optimal treatment of hypothyroidism and subclinical hypothyroidism in pregnancy is less certain however. What interventions are available? Which interventions, evaluated in carefully conducted randomised trials, significantly improve maternal, fetal and infant outcomes? Do these interventions have any clinically significant adverse outcomes? Given the mounting evidence of associated long-term negative sequelae for the offspring of women with peripartum thyroid deficiency, there is increasing pressure to identify the most effective and safe interventions for treating clinical and subclinical hypothyroidism prior to, and during pregnancy.

Criteria for considering studies for this review

Types of studies
Randomised controlled trials or quasi-randomised trials that compared an intervention for hypothyroidism and/or subclinical hypothyroidism pre-pregnancy or during pregnancy with another intervention or placebo. We planned to include cluster-randomised trials, and studies published as abstracts only. We planned to exclude cross-over trials.

Types of participants
Pregnant women with a diagnosis (either pre-pregnancy or during pregnancy) of hypothyroidism, subclinical hypothyroidism or isolated maternal hypothyroxinaemia.

Types of interventions
We included any pharmacological intervention used for hypothyroidism, subclinical hypothyroidism or isolated maternal hypothyroxinaemia pre-pregnancy or during pregnancy. One intervention could be compared with another or with placebo and combinations of therapy could be used.

Types of outcome measures

Primary outcomes
Maternal
- Pre-eclampsia (variously defined)

Infant
- Preterm birth (defined as birth less than 37 weeks’ gestation)

Secondary outcomes

Maternal
- Symptomatic hypothyroidism (defined in background)
- Gestational hypertension (variously defined)
- Excessive weight gain in pregnancy (variously defined)
- Anaemia (defined as a reduction in the quantity of haemoglobin and red blood cells in the blood)
Placental abruption (defined as premature separation of a normally situated placenta from the uterus in the second half of pregnancy)
Preterm labour (defined as the onset of regular uterine contractions and cervical dilatation less than 37 weeks' gestation)
Postpartum haemorrhage (defined as blood loss of more than or equal to 500 mL within six weeks of giving birth)
Postpartum depression (defined as a depressive illness that commences or continues throughout the first postpartum year - diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders (DSM) IV Criteria)
Maternal death (defined as the death of a woman while pregnant or within 42 days of the termination of pregnancy, from any cause related to, or aggravated by, pregnancy or its management, excluding accidental or incidental causes)
Quality of life (variously defined)
Infertility (defined as one year of unprotected intercourse without pregnancy)

Fetal/neonatal/infant
Death (defined as all fetal or neonatal deaths)
Fetal death (variously defined), including miscarriage (defined as loss of a pregnancy prior to the embryo or fetus being viable)
Neonatal death (variously defined)
Small for gestational age (defined as birthweight less than 10th centile)
Admission to special care (variously defined)
Cretinism (defined as congenital hypothyroidism resulting in impaired physical and mental development)
Goitre (defined as chronic enlargement of the thyroid gland)
Jaundice requiring phototherapy (elevation of bilirubin in the neonatal blood requiring phototherapy)
Poor feeding (variously defined)
Constipation (variously defined)
Hoarse cry (variously defined)
Lethargy (variously defined)
Hypotonia (defined as a diminution or loss of muscular tonicity)
Macroglossia (defined as enlargement of the tongue)
Umbilical hernia (defined as protrusion of abdominal contents through the abdominal wall under the skin at the umbilicus)
Patent fontanelles (variously defined)

Health services
Maternal length of hospital stay (in days)
Neonatal length of hospital stay (in days)
Cost of services

Safety of interventions (adverse effects)

Search methods for identification of studies

Electronic searches
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 March 2013). 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;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.
Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We did not apply any language restrictions.

Data collection and analysis

Selection of studies
Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion and where necessary, by involving a third author.
**Data extraction and management**

We designed a form to extract data (based on the data extraction template of the Cochrane Pregnancy and Childbirth Group). For eligible studies, two review authors extracted the data using the agreed form. We resolved any discrepancies through discussion or, if required, we consulted a third review author. We entered data into Review Manager software (RevMan 2011) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

**Assessment of risk of bias in included studies**

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

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

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

We assessed the methods 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 described for each included study the method used to conceal the allocation sequence and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

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

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

We assessed 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 described for each included study and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, 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 was reported or was supplied by the trial authors, we included missing data in the analyses which we undertook.

We assessed the methods as:

- low risk of bias (e.g. where there was no missing data or where reasons for missing data were 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.

**(5) Selective reporting bias (checking for reporting bias)**

We described for each included study how the possibility of selective outcome reporting bias was examined by us and what we found.

We assessed the methods as:

- low risk of bias (where it was clear that all of the study’s prespecified outcomes and all expected outcomes of interest to the review had been reported);
- high risk of bias (where not all the study’s prespecified outcomes had been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to
include results of a key outcome that would have been expected to have been reported;

• unclear risk of bias.

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

We described for each included study any important concerns we had about other possible sources of bias. We assessed 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 made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

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

Where women did not become pregnant, any data provided on outcomes included in the review would have been reported and these women would be excluded from outcomes that could not be applied to them, such as where pregnancy was implied.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually-randomised trials. We would have adjusted their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we had used ICCs from other sources, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We planned to consider it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely. We planned to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

We considered cross-over designs inappropriate for this research question.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to 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 carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were 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 was the number randomised minus any participants whose outcomes were known to be missing.

In those studies where women were recruited preconception, for outcomes relating to pregnancy, we planned to take a pragmatic approach and include in the denominators only those women known to have become pregnant.

Assessment of heterogeneity

If we had pooled studies, we planned to assess statistical heterogeneity in each meta-analysis using the $T^2$, $I^2$ and $\chi^2$ statistics. We planned to regard heterogeneity as substantial if the $I^2$ was greater than 30% and either the $T^2$ was greater than zero, or there was a low $P$ value (less than 0.10) in the $\chi^2$ test for heterogeneity.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we planned to investigate reporting biases (such as publication bias) using funnel plots. We planned to assess funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.
Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We planned to treat the random-effects summary as the average range of possible treatment effects and we planned to discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we planned not to combine trials.

If we had used random-effects analyses, we planned to present the results as the average treatment effect with 95% confidence intervals, and the estimates of $T^2$ and $I^2$.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Severity of disease (overt hypothyroidism versus subclinical hypothyroidism versus isolated maternal hypothyroxinaemia).
2. Type and dosage of intervention (e.g. thyroxine versus selenium versus iodine).
3. Timing of the randomisation and when the intervention commenced (pre-conception versus first trimester versus second trimester versus third trimester).

We planned to restrict analysis to primary outcomes only.

We planned to assess subgroup differences by interaction tests available within RevMan (RevMan 2011). We planned to report the results of subgroup analyses quoting the $\chi^2$ statistic and $P$ value, and the interaction test $I^2$ value.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effects of trial quality by allocation concealment and other risk of bias components, by omitting studies rated as high risk of bias for these components. We planned to restrict sensitivity analyses to the primary outcomes. We performed an analysis with and without post-randomisation exclusions for miscarriage.

Results of the search

The updated search identified three potentially eligible studies (Negro 2010; Petri 2011; Yassa 2010). We included one of the trials (Yassa 2010), and excluded two from the review (Negro 2010; Petri 2011). An additional reference was found for a previously ongoing study and this resulted in the study being excluded (Lazarus 2012). Overall, we included four trials in this review (Negro 2006; Negro 2007; Rotondi 2004; Yassa 2010). We excluded four trials as they did not meet the inclusion criteria (Harris 2002; Lazarus 2012; Negro 2010; Petri 2011).

One randomised trial is ongoing (Spong 2008). Pregnant women at less than 20 weeks' gestation with subclinical hypothyroidism or hypothyroxinaemia are eligible for this trial and will be randomised to either levothyroxine or placebo until delivery. The primary outcome of the trial is intellectual function of the children at five years of age, and a number of perinatal outcomes are being assessed. The trial is expected to be completed in May 2014. For further details, see Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies.

Included studies

We included four randomised studies involving 362 women (Negro 2006; Negro 2007; Rotondi 2004; Yassa 2010). Three of the trials were conducted in Italy (Negro 2006; Negro 2007; Rotondi 2004), a country still characterised by moderate iodine deficiency as iodised salt is not compulsory by law. These trials explored two interventions for hypothyroidism - levothyroxine (Negro 2006; Rotondi 2004) and selenomethionine (selenium) (Negro 2007). Levothyroxine was compared with no treatment or with no change in treatment during the pregnancy (Negro 2006; Rotondi 2004) and selenium was compared with placebo (Negro 2007). The fourth trial took place in a hospital and university department in the United States of America and explored the impact of levothyroxine dosage adjustment on biochemical thyroid function (Yassa 2010).

Negro 2006 evaluated 984 pregnant women for autoimmune thyroid disease. Women were not eligible if they had pre-existing thyroid dysfunction. One-hundred and fifteen participants who were thyroid peroxidase antibody positive (11.7%) were randomised into two groups. The intervention group was commenced on levothyroxine at the first endocrinological consultation and the medication was continued throughout the pregnancy. The control group received no treatment. The dosage of levothyroxine varied depending on TSH and thyroid peroxidase antibody titres. The rates of obstetric complications including gestational hypertension, severe pre-eclampsia and preterm birth, as well as serum TSH and free T4 were measured. Other outcomes including miscarriage, abortion and clinical characteristics of the newborns were also reported by Negro et al, although these were not prespecified.

Description of studies
In a separate trial, another cohort of euthyroid pregnant women positive for thyroid peroxidase antibodies were studied by Negro et al (Negro 2007). Of the 2143 women, 7.9% were found to be thyroid peroxidase antibody positive. This study examined a different intervention - selenium - and considered whether supplementation would reduce the rate of postpartum thyroid dysfunction (PPTD) and permanent hypothyroidism. Participants were randomised into two groups and either selenium 200µg/day or placebo was administered at or after 12 weeks’ gestation. All the women in this study were advised to use iodised salt. Thyroid function tests were performed at 20 and 30 weeks, at delivery and monthly one to two, five, nine and 12 postpartum. Levothyroxine treatment was commenced if participants had TSH concentrations above the normal range and/or free T4 concentrations below the normal range. At 12 months postpartum, patients on levothyroxine stopped receiving this substitutive therapy, to determine whether their hypothyroidism was permanent. Selenium concentrations were measured at the first visit (mean 9.4 (+/- 2.7) µg/L) at 20 and 30 weeks’ gestation, at delivery and six and 12 months postpartum. Participants also underwent thyroid ultrasound scanning to assess for thyroiditis by an independent radiologist at the first visit, at delivery and at 12 months postpartum. A third smaller trial included in this review assessed levothyroxine as an intervention for hypothyroidism. In this study by Rotondi et al (Rotondi 2004), 25 women with hypothyroidism of differing aetiology who were anticipating pregnancy (and subsequently became pregnant) and taking substitutive doses of levothyroxine were assigned to two groups. In Group 1 (modified n = 15), the levothyroxine dose was adjusted to maintain low-normal serum TSH concentrations. Group 1 included four women with Hashimoto’s thyroiditis and 11 women who had been thyroidectomised. Group 2 (unmodified n = 15) continued the same therapeutic regimen and included five women with Hashimoto’s thyroiditis and 10 women who had been thyroidectomised. Thyroid function tests were performed pre-conception (at least 60 days from the levothyroxine increase for the Group 1 participants) and at the first post-conception endocrinological visit (median seven weeks’ gestation). Rotondi et al assessed biochemical outcome measures, specifically serum free T3, free T4 and TSH titres. TSH titres were the primary endpoint of the fourth trial by Yassa et al (Yassa 2010), which evaluated the effectiveness of levothyroxine dosage adjustment in preventing maternal hypothyroidism. Women were eligible if they had treated primary hypothyroidism, were seeking pregnancy or less than 11 weeks’ gestation and had been receiving a stable dose of levothyroxine for at least six weeks. Women were randomised upon confirmation of pregnancy. Group A (n = 25) were randomised to receive two extra tablets per week (29% increase) and Group B (n = 23) were randomised to increase their levothyroxine by three extra tablets per week (43% increase). Both groups included women with a history of thyroid cancer and surgery, Hashimoto’s thyroiditis or radioactive iodine ablation. After initiation of increased supplementation, participants underwent thyroid function testing fortnightly and levothyroxine dose was modified every four weeks (weeks 4, 8, 12, 16, 20 and 30). On the intervening weeks (week 6, 10, 14 and 18), dosage was only modified if TSH was greater than 10 mIU/L or less than 0.1 mIU/L.

**Excluded studies**

Harris 2002 investigated the hypothesis that stabilising thyroid function postpartum would reduce the occurrence and severity of postpartum depression. Harris et al concluded that there was no evidence that thyroxine had any effect on the occurrence of depression. We excluded this trial as the participants did not meet the criteria for this review, as they were no longer pregnant when the intervention took place.

Lazarus 2012 evaluated screening of thyroid function in early pregnancy. This multi-centre, randomised controlled trial set in the United Kingdom recruited women with singleton pregnancies before 16 weeks. Serum TSH and T4 tittes were obtained at randomisation and participants were allocated to ‘screen’ group (thyroid function testing at randomisation, with thyroxine intervention if required) and ‘control’ group (thyroid function testing measured post delivery, with thyroxine intervention if required). We excluded this trial as it included all pregnant women, not pregnant women with a diagnosis of hypothyroidism, subclinical hypothyroidism or isolated maternal hypothyroxaemia as per review criteria.

A further randomised trial (Negro 2010) was excluded on the same basis, as the study included all pregnant women (i.e. those with no history of thyroid disease). The women were randomly assigned during their first trimester to universal thyroid screening or to a control group. All participants were stratified as high risk or low risk based on thyroid disease risks factors and if high risk, they were tested for free T4, TSH and thyroid peroxidase antibody and treated with levothyroxine if deemed to be hypo- or hyperthyroid. Negro et al concluded that low-risk women in the screening group were less likely to suffer obstetric and neonatal adverse outcomes, but that universal screening did not result in a decrease in adverse outcomes.

The final trial that we excluded, Petri 2011 was withdrawn as per Clinical Trial.gov http://clinicaltrials.gov/ct2/show/NCT01276782 because “further analysis showed that it would be futile”. The study was to be a pilot randomised clinical trial looking at thyroxine for autoimmune thyroid disease in systemic lupus erythematosus in pregnancy.

**Risk of bias in included studies**

Overall, the risk of bias was judged to be moderate - see Characteristics of included studies, Figure 1 and Figure 2 for further details.
Figure 1. Methodological quality graph: review authors’ judgements about each methodological quality item presented as percentages across all included studies.
Figure 2. Methodological quality summary: review authors’ judgements about each methodological quality item for each included study.
**Allocation**

Three trials used adequate methods to generate a random sequence (Negro 2006; Negro 2007; Rotondi 2004), each using a computer-generated randomisation sequence. In Yassa 2010, no detail was provided regarding the randomisation sequence. All trials were judged to be at an unclear risk of selection bias with the methods used to conceal allocation being unclear. In Negro 2006 and Negro 2007, sealed, opaque envelopes were used, however, it was not specified whether they were assigned in consecutive order (or numbered consecutively). In Rotondi 2004, and Yassa 2010, methods to conceal allocation were not detailed.

**Blinding**

Three trials were judged to be at a high risk of performance bias, with no blinding of participants (Negro 2006; Rotondi 2004; Yassa 2010). In Negro 2007, the participants were blinded with the use of a placebo, and thus the trial was judged to be at a low risk of performance bias. For all four trials the blinding of personnel and outcome assessors was unclear (Negro 2006; Negro 2007; Rotondi 2004; Yassa 2010), and thus the trials were judged to be at an unclear risk of detection bias.

**Incomplete outcome data**

Two trials were judged to be at a low risk of bias due to attritions and exclusions. In Rotondi 2004, no participants were lost to follow-up in the modified group, and in the unmodified group, only two women were lost. In Negro 2006 outcome data were missing only for women who had suffered a miscarriage.

The two remaining trials were judged to be at an unclear risk of bias. In Negro 2007, eight women were lost to follow-up (six due to miscarriage, two for personal reasons) in the selenium group, and 10 in the placebo group (seven due to miscarriage, three for personal reasons); the authors excluded the 18/169 women from the analyses, and intention-to-treat analyses were not performed. In Yassa 2010, analyses were performed on 48/60 women “enrolled” in the study; six participants were excluded due to miscarriage after enrolment, but reportedly prior to randomisation. There were six additional participants excluded after randomisation (four secondary to miscarriage, one due to molar pregnancy and one due to stillbirth), and these women were also excluded from the analyses.

**Selective reporting**

Negro 2007 was judged to be at a low risk of reporting bias - whilst exact figures for some outcome measures were not reported in the trial manuscript, these were supplied by the trial authors on request. The three other trials (Negro 2006; Rotondi 2004; Yassa 2010) were judged to be at an unclear risk of reporting bias. In Negro 2006, a number of outcomes, such as miscarriage, placental abruption and clinical characteristics of the newborns were not prespecified. In Yassa 2010, no relevant clinical outcome were reported, and whilst miscarriages were detailed in text (relating to those women ‘excluded’ from analyses), the numbers per group were not reported. Rotondi 2004, similarly did not report any relevant clinical outcome data.

**Other potential sources of bias**

All four trials were judged to be at low risk of other potential bias, with no obvious sources of bias identified.

**Effects of interventions**

1. **Levothyroxine versus no treatment**

One trial of 115 women compared levothyroxine with no treatment (Negro 2006).

**Primary outcomes**

**Pre-eclampsia**

Antenatal treatment of thyroid peroxidase antibody positive women with levothyroxine was not shown to reduce pre-eclampsia significantly (risk ratio (RR) 0.61; 95% confidence interval (CI) 0.11 to 3.48); see Analysis 1.1.

**Preterm birth**

Levothyroxine significantly reduced preterm birth by 72% (RR 0.28; 95% CI 0.10 to 0.80) see Analysis 1.2. In this trial, the levothyroxine group had a preterm birth rate of 7.2% compared with a preterm rate of 26% in the untreated group (risk difference (RD) -0.19; 95% CI -0.33 to -0.05). Negro 2006 did not report our third primary outcome, neurodevelopmental delay.

**Secondary outcomes**

**Miscarriage**

There was a trend towards reduced risk of miscarriage with levothyroxine compared with no treatment (P = 0.07), although this did not reach statistical significance (RR 0.25; 95% CI 0.06 to 1.15).
see Analysis 1.3. Women in the levothyroxine group had a miscarriage rate of 3.5%, whereas the rate of miscarriage in the untreated group was 13.7% (RD -0.10; 95% CI -0.20 to -0.00). We performed sensitivity analysis with and without post-randomisation exclusions; both produced very similar results.

**Secondary outcomes**

**Miscarriage**

No significant difference in the rate of miscarriage was seen between selenium and placebo (RR 0.85; 95% CI 0.30 to 2.42); see Analysis 2.3.

**Symptomatic hypothyroidism**

Negro 2007 evaluated the influence of selenium on postpartum hypothyroidism in previously euthyroid thyroid peroxidase antibody positive women. No difference was seen between the selenium and placebo groups for hypothyroidism two months after stopping levothyroxine (RR 0.77; 95% CI 0.21 to 2.75); see Analysis 2.4. Selenium reduced postpartum thyroid dysfunction (within 12 months of delivery) by 41% (RR 0.59; 95% CI 0.38 to 0.90); see Analysis 2.5; 28.6% of women in the selenium group and 48.6% of women in the placebo group developed thyroid dysfunction postpartum (RD -0.20; 95% CI -0.35 to -0.05). Selenium also showed some favourable impact on the incidence of permanent hypothyroidism (as measured 12 months post delivery). Women in the selenium group had a 11.7% rate of hypothyroidism, whereas the rate of hypothyroidism in the placebo group was 20.3% (RD -0.09; 95% CI -0.20 to 0.03), although this did not reach statistical significance (RR 0.58; 95% CI 0.27 to 1.24); see Analysis 2.6.

**Gestational hypertension**

No significant difference in the rate of gestational hypertension was seen between selenium and placebo, however, exact figures were not reported.

**Placental abruption**

The rate of abruption did not vary significantly despite treatment with selenium, however, exact figures were not reported.

**Thyroiditis (not prespecified in our protocol)**

This outcome measure was not prespecified in the protocol for this systematic review, however, it was considered important to include given the findings by Negro 2007. An independent radiologist performed high resolution thyroid ultrasound scanning at the end of the postpartum period (12 months after delivery) and classified thyroid parenchyma as normal, mild, moderate or advanced thyroiditis. Of the women receiving selenium, 72.7% were classified as mild or no thyroiditis, compared with 55.4% of women receiving placebo. Therefore, the selenium supplemented group displayed a significantly reduced rate of moderate and advanced thyroiditis (27.3%, compared with 44.6% in the placebo group).
Selenium significantly reduced postpartum thyroiditis (moderate or advanced) by 39% (RR 0.61; 95% CI 0.39 to 0.95) compared with placebo (see Analysis 2.7). There was no significant difference when mild thyroiditis was included in the overall analysis (RR 1.00; 95% CI 0.90 to 1.12); see Analysis 2.8.

Negro 2007 did not report on any of the review’s other secondary outcomes.

Given the paucity of data, and the different comparisons, we were unable to carry out the meta-analyses or subgroup analyses as planned.

**Discussion**

**Summary of main results**

Four randomised controlled trials including 362 women and their babies were included in this review (Negro 2006; Negro 2007; Rotondi 2004; Yassa 2010), however, only two of the included trials provided data on the review’s prespecified outcomes (Negro 2006; Negro 2007).

Of the two trials that reported on the outcome pre-eclampsia in pregnancies of thyroid peroxidase antibody positive (TPOAb+) women (Negro 2006; Negro 2007), there was no significant reduction with levothyroxine treatment, nor with selenium treatment. This is in contrast to an earlier prospective cohort study of 68 participants (Leung 1993) which reported that gestational hypertension (including pre-eclampsia, eclampsia and pregnancy-induced hypertension) was significantly more common in those with untreated subclinical and clinical hypothyroidism. Given that Negro studied two euthyroid populations, it is quite possible that pre-eclampsia is a manifestation of more severe thyroid disease in pregnancy.

The review showed a relative reduction in preterm delivery with levothyroxine treatment in euthyroid TPOAb+ women in one trial (RR 0.28; 95% CI 0.10 to 0.80). This result from Negro 2006 is in keeping with previous findings documented in reviews (Lazarus 2005) and clinical guidelines (Abalovich 2007) and correlates with the known increased rate of maternal complications in women with hypothyroidism. Preterm birth is common, often devastating and proven interventions for prevention are few and far between; thus this finding provides some promising evidence for an intervention that may be of benefit to a specific population of women. No reduction in preterm birth was shown in Negro 2007 with selenium treatment in euthyroid TPOAb+ women.

Neither Negro 2006 nor Negro 2007 assessed the effects of levothyroxine or selenium treatment on the review’s third primary outcome: neurodevelopmental delay. Evidence of a possible reduction in miscarriage with levothyroxine treatment for euthyroid TPOAb+ women was revealed in Negro 2006. A trend towards reduced miscarriage was shown for women receiving levothyroxine compared with women who received no treatment (P = 0.07). No reduction in miscarriage was shown in Negro 2007, when women were treated with selenium.

Considering postpartum thyroid dysfunction, Premawardhana 2000 previously concluded that dysfunction occurs in up to 50% of women with thyroid peroxidase antibodies in early pregnancy. Negro 2007 reported a comparable figure of 48.6% in women who were TPOAb+ and received placebo. Of the TPOAb+ women who received selenium, 28.6% suffered thyroid dysfunction postpartum - a relative reduction of 41%. Selenium was also demonstrated to significantly reduce moderate-to-severe postpartum thyroiditis (a 39% relative reduction). The degree of thyroiditis was assigned by an independent radiologist, depending on the echogenicity of the thyroid parenchyma. A more robust classification of thyroiditis is proposed, given the possibility for inter-observer variation. However, given the high incidence of permanent hypothyroidism described in women with postpartum thyroid dysfunction, its prevention may lead to significant health benefits, especially in future pregnancies.

No reduction in gestational hypertension or placental abruption was shown when TPOAb+ women were treated with either levothyroxine or selenium (Negro 2006; Negro 2007), and neither Negro 2006 nor Negro 2007 reported on the other secondary outcomes of this review.

Negro 2007 appears to be the first intervention trial to assess selenium in pregnancy. No adverse effects were identified, but as with any novel intervention, caution is recommended. Selenium is known to have a regulatory role in the activation and inactivation of thyroid hormones. Prior reports have found that in areas of considerable selenium and iodine deficiency, selenium supplementation in hypothyroid patients reduced thyroid hormone concentrations dramatically (Contempre 1993). This could have obvious adverse maternal-fetal effects and therefore selenium treatment should be confined to large-scale randomised intervention trials until its safety is confirmed.

Preconceptual levothyroxine treatment was studied by Rotondi 2004, however, unfortunately none of our prespecified outcomes were reported. Similarly, Yassa 2010 assessed levothyroxine (pre-conception and during pregnancy), however, reported on none of the outcomes for the review. Rotondi 2004 concluded that in hypothyroid women with TSH concentrations in the lower quartile of normal range, a preconception adjustment of levothyroxine may result in adequate thyroid function in early pregnancy. Women receiving partially suppressive therapy had significantly higher FT4 and lower TSH than those receiving replacement levothyroxine doses. Yassa 2010 concluded that in hypothyroid women, a twotable per week (29%) increase in levothyroxine initiated at the confirmation of pregnancy (less than 11 weeks gestation) significantly reduces the risk of maternal hypothyroidism during the first trimester (preventing maternal TSH elevation over 2.5 mIU/L and over 5.0 mIU/L in 85% and 100% respectively), and mimics normal physiology. Whether such biochemical improvements
result in improved obstetric outcomes remains to be seen, however, preconceptional optimisation of thyroid function may prove worthwhile.

Iodine is an important intervention in preventing adverse outcomes of maternal hypothyroidism and is discussed in two other Cochrane reviews. Briefly, it should be noted that three of the trials were conducted in Italy, a country where iodised salt is not compulsory by law and where there is moderate iodine deficiency. It could be argued that in iodine-sufficient populations, the impact of levothyroxine and selenium on adverse pregnancy outcomes would be less. Worldwide, most cases of maternal hypothyroxinaemia are related to iodine deficiency - would adequate iodine supplementation through iodised salt, bread, water, oil and iodine tablets be sufficient? Whist treatment of clinical hypothyroidism with levothyroxine is logical, the roles of levothyroxine and selenium in subclinical thyroid dysfunction needs further clarification.

Overall completeness and applicability of evidence

There is a significant lack of randomised trials in this area. Many important adverse pregnancy outcomes associated with clinical and subclinical hypothyroidism have never been measured in intervention trials.

This review is limited with the inclusion of four small trials (including 362 women and their babies), of which only two trials, involving 284 women contributed data to this review. While the two trials did report on pre-eclampsia and preterm birth, neither trial reported on the review’s third primary outcome - neurodevelopmental delay. Given the likely association of clinical and subclinical hypothyroidism with fetal neurological damage and later childhood disability, there is a particular need for trials in this area to assess this important outcome.

The two trials that did contribute data to the review did not report on many of the additionally important secondary review outcomes, including excessive weight gain in pregnancy, anaemia, postpartum haemorrhage, postpartum depression, quality of life, infertility, and a variety of infant outcomes. Neither trial reported on the use or cost of health services.

A further limitation of this review is that both trials that contributed data to the review included only euthyroid TPOAb+ women, and therefore this review does not include data regarding women with other important causes of primary and secondary hypothyroidism (for example, women with who have undergone a thyroidectomy, or who are being treated for thyroid cancer).

For further completeness, we are awaiting completion of an ongoing large-scale randomised trial (Spong 2008), which is recruiting women with subclinical hypothyroidism or hypothyroxinaemia diagnosed during pregnancy.

Quality of the evidence

The quality of the evidence was judged to be low to moderate (with a moderate risk of bias overall). Both studies from which we could obtain clinical outcome data had relatively small sample sizes and methodological limitations, including unclear concealment of allocation and thus unclear risk of selection bias. Three of the four included studies were judged at high risk of performance bias with no blinding of participants; in only one of the four trials was a placebo used. The risk of detection bias was judged as unclear across all four trials.

Authors’ conclusions

Implications for practice

There are currently insufficient data in this review to support any recommendations for practice for the treatment of clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy.

Levothyroxine treatment of clinical hypothyroidism in pregnancy, where iodine nutrition is adequate, is already standard practice given the documented benefits from earlier prospective and retrospective cohort studies. Obtaining and maintaining a euthyroid state from conception may maximise these benefits, particularly in the case of reducing first trimester miscarriage rates. Preconceptual and early pregnancy counselling regarding the importance of thyroid hormone control in reducing significant maternal-fetal morbidity, such as preterm birth, is currently advisable. Subclinical hypothyroidism may adversely affect the mother and developing fetus with long-term repercussions and The Endocrine Society Clinical Practice Guidelines (Abalovich 2007) already recommend levothyroxine replacement. Evidence from the randomised controlled trials included in this review however, did not provide evidence to support, nor to refute, this current practice.

Selenomethionine as an intervention in women with thyroid autoantibodies is promising, particularly in reducing moderate to severe postpartum thyroiditis, benefiting women and their future pregnancies. Evidence from this review, however, is insufficient to guide practice.

Implications for research

There is a need for larger randomised trials to assess the efficacy and safety of interventions for both clinical and subclinical hypothyroidism of pregnancy. Further high-quality evidence would clarify the role of levothyroxine replacement in subclinical hypothyroidism.

Questions remain, such as the optimal reference ranges for thyroid function tests in pregnancy, the magnitude of benefit of treatment versus no treatment - especially in subclinical hypothyroidism, and
whether there could be significant adverse effects of levothyroxine or selenomethionine.

The ideal randomised trial would study women of reproductive age with clinical and subclinical hypothyroidism, as well as women with thyroid autoantibodies given their prevalence. The trial would recruit women preconceptually, have an appropriate sample size, include a placebo arm and adequately blind the participants, clinicians and outcome assessors. There is a need for both interventions identified by this review - levothyroxine and selenomethionine, to be studied in further depth. Data on common and clinically important outcomes should be gathered, including any adverse effects of treatment. Long-term follow-up of the participants and their offspring is essential given the important association between hypothyroidism and impaired childhood neuropsychological development. Subgroups such as autoimmune versus subclinical versus clinical hypothyroidism and the optimal type, dosage and timing of the intervention should be explored. Populations such as women with a history of preterm birth, recurrent miscarriage or significant postpartum thyroid dysfunction should be specifically included in randomised controlled trials. One such large-scale intervention trial is underway (Spong 2008).

ACKNOWLEDGEMENTS

We thank Roberto Negro (author of Negro 2007) for his correspondence, and for providing additional information to enable outcome data to be included in the review.

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REFERENCES

References to studies included in this review

Negro 2006 [published and unpublished data]

Negro 2007 [published and unpublished data]

Rotondi 2004 [published and unpublished data]

Yassa 2010 [published data only]

References to studies excluded from this review

Harris 2002 [published and unpublished data]

Lazarus 2012 [published and unpublished data]

Negro 2010 [published data only]

Petri 2011 [unpublished data only]

References to ongoing studies

Spong 2008 [unpublished data only]

Additional references

Abalovich 2002
Abalovich 2007

Angermayr 2004

Cao 1994

Casey 2006

Casey 2007

Cleary-Goldman 2006

Contempre 1993

Davis 1988

Gharib 2005

Haddow 1999

Harborne 2004

Higgins 2011

Jameson 2008

Lazarus 2005

Leung 1993

Man 1969

McElduff 2008

Pop 1999

Premawardhana 2000

RevMan 2011

Wu 2002

References to other published versions of this review
Reid 2010


* Indicates the major publication for the study
### Characteristics of included studies  
*ordered by study ID*

**Negro 2006**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial, set in a hospital department of obstetrics and gynaecology in Italy</th>
</tr>
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<tbody>
<tr>
<td>Participants</td>
<td>Pregnant women testing positive (&gt; 100 kIU/L) for thyroid peroxidase antibodies. Exclusion criteria: overt hypothyroidism or pre-existing thyroid dysfunction. 115 TPOAb+ women were randomised (57 to levothyroxine (LT) and 58 to no treatment). 2 miscarriages in the LT group and 8 in the no treatment group, thus giving denominators of 55 and 50 women respectively.</td>
</tr>
<tr>
<td>Interventions</td>
<td>LT treatment versus no treatment. Dose of LT: 0.5 $\mu$g/kg/d if TSH &lt; 1.0 mIU/L; 0.75 $\mu$g/kg/d if TSH between 1.0 and 2.0 mIU/L; 1 $\mu$g/kg/d if TSH &gt; 2.0 mIU/L or a TPOAb titre exceeding 1500 kIU/L.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Gestational hypertension (defined as intrapartum systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg). Severe preeclampsia (women with hypertension with at least one of the following: blood pressure higher than 160/110 mmHg, serum creatinine greater than 1.0 mg/dL, a platelet count less than 100,000/$\mu$L, serum aspartate aminotransferase concentration at least twice the normal value, persistent headache or scotoma, 2+ or greater proteinuria, or more than 2 g protein excreted in 24 hours). Preterm birth (&lt; 37 weeks). Serum TSH and free T4. Miscarriages. Abruptio. Clinical characteristics of newborns (weight, height, cranial perimeter, Apgar score).</td>
</tr>
<tr>
<td>Notes</td>
<td>Age range: LT group mean 30 (SD 5); no treatment group 30 (SD 6) years. First endocrinological visit: LT group: 10.4 (3.1) weeks; no treatment group: 10.3 (3.1) weeks. LT administered in treatment group: 49.7 (14) $\mu$g/d. 8 women received 0.5 $\mu$g/kg/d (30.6 (4.9) $\mu$g/d). 35 women received 0.75 $\mu$g/kg/d (47.7 (6.0) $\mu$g/d). 14 women received 1.0 $\mu$g/kg/d (64.7 (8.7) $\mu$g/d). Gestational ages when treatment was started were similar in the 3 subgroups (9.6 (5); 10.1 (3.7) and 10.9 (3.8) weeks, respectively). 869 TPOAb- women served as a non-randomised, normal control group.</td>
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#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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### Negro 2006  
(Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Level</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>A computer program was used to randomly assign the TPOAb+ patients to either the intervention group or control group</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>A sealed opaque envelope was assigned to each patient, but not specified if consecutive envelopes</td>
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<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>No placebo was used.</td>
</tr>
<tr>
<td>Participant</td>
<td></td>
<td>Doctors participated in different phases of the study, so that each was unaware of group allocations</td>
</tr>
<tr>
<td>Clinician</td>
<td>Unclear risk</td>
<td>Could not determine.</td>
</tr>
<tr>
<td>Outcome Assessor</td>
<td>Unclear risk</td>
<td>Adequate as all missing data were due to miscarriages (2 women suffered 1st trimester miscarriage in the LT group, 8 in the no treatment group)</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Adequate as all missing data were due to miscarriages (2 women suffered 1st trimester miscarriage in the LT group, 8 in the no treatment group)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Some outcomes not prespecified (i.e. miscarriage, abruption, clinical characteristics of newborns)</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>We were not able to detect any other sources of bias.</td>
</tr>
</tbody>
</table>

### Negro 2007

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective, parallel randomised placebo-controlled trial, set in a hospital department of Obstetrics and Gynaecology and Endocrinology in Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Euthyroid women positive for thyroid peroxidase antibodies. 169 women were randomised (85 to Selenomethionine (Se) and 84 to placebo) - providing the denominators for the outcome of miscarriage. This reduced to 77 in the Se group (6 miscarriages and 2 withdrawals) and 74 in the placebo group (7 miscarriages and 3 withdrawals) - providing the denominators for the later outcomes</td>
</tr>
<tr>
<td>Interventions</td>
<td>Selenomethionine (200 µg/day) administered at or after 12 weeks’ gestation versus placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>Permanent hypothyroidism.</td>
<td>Postpartum thyroid dysfunction.</td>
</tr>
<tr>
<td>TSH, free T4, TPOAb serum concentrations.</td>
<td>Thyroid ultrasound - echogenicity of parenchyma classified as</td>
</tr>
<tr>
<td></td>
<td>normal (Grade 0) or mild thyroiditis (Grade 1), moderate</td>
</tr>
<tr>
<td></td>
<td>thyroiditis (Grade 2) or severe thyroiditis (Grade 3).</td>
</tr>
<tr>
<td>Cysts and nodules disregarded</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper does not report when the 5 women withdrew.</td>
<td>TPOAb- women served as a non-randomised control group.</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>A sealed opaque</td>
</tr>
<tr>
<td></td>
<td></td>
<td>envelope was assigned</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to each patient, but</td>
</tr>
<tr>
<td></td>
<td></td>
<td>not specified if</td>
</tr>
<tr>
<td></td>
<td></td>
<td>consecutive envelopes</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Placebo-controlled.</td>
</tr>
<tr>
<td>Participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Could not determine.</td>
</tr>
<tr>
<td>Clinician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Could not determine.</td>
</tr>
<tr>
<td>Outcome Assessor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>169 women were</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>randomised (85 to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Se-lengthomethionine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Se) and 84 to placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- providing the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>denominators for the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>outcome of miscarriage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This reduced to 77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in the Se group (6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>miscarriages and 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>withdrawals) and 74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in the placebo group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7 miscarriages and 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>withdrawals) -</td>
</tr>
<tr>
<td></td>
<td></td>
<td>providing the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>denominators for the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>later outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Therefore some missing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>data due to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>miscarriages and 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>randomised women lost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Not all exact figures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reported, but supplied</td>
</tr>
<tr>
<td></td>
<td></td>
<td>when contacted.</td>
</tr>
</tbody>
</table>
### Negro 2007  
*(Continued)*

<table>
<thead>
<tr>
<th>Other bias</th>
<th>Low risk</th>
<th>Free of baseline characteristic imbalance and we were not able to detect any other sources of bias</th>
</tr>
</thead>
</table>

### Rotondi 2004

**Methods**  
Prospective parallel randomised trial, set in a university department of surgery and endocrinology in Italy

**Participants**  
Women under LT replacement therapy for primary hypothyroidism (21 women had undergone thyroidectomy for non-toxic multinodular goitre; 9 women had a clinical and biochemical diagnosis of hypothyroid Hashimoto’s thyroiditis) planning a pregnancy in the next 12 months and less than 12 weeks' gestation at the first post-conception consultation (median 7 weeks)

**Interventions**  
Women were assigned to 2 groups and Group 1 (modified group n = 15; 11 thyroidectomised, 4 with Hashimoto's thyroiditis) had their levothyroxine dosage adjusted to maintain low-normal serum TSH concentrations. Group 2 (unmodified n = 15; 10 thyroidectomised, 5 with Hashimoto's thyroiditis) continued their usual therapeutic regimen

**Outcomes**  
Free T4.  
Free T3.  
TSH.

**Notes**  
Of the 30 women who were randomised, 25 pregnant women were included in the ‘post-conception’ study group; 5 women “missed evaluation” during pregnancy from Group 2: 2 who were lost to follow-up, 2 who did not become pregnancy, and 1 who was already 23 weeks gestation at the first post-conception consultation

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer randomisation and stratification.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Could not determine.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) Participant</td>
<td>High risk</td>
<td>No placebo.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) Clinician</td>
<td>Unclear risk</td>
<td>Could not determine.</td>
</tr>
</tbody>
</table>
Rotondi 2004  (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding (performance bias and detection bias) Outcome Assessor</td>
<td>Unclear risk</td>
<td>Could not determine.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Modified group: none lost to follow-up, one woman was shifted to the unmodified group Unmodified group: 5 missed evaluation during pregnancy (2 lost to follow-up, 2 decided not to become pregnant and 1 woman was not seen prior to 12 weeks' gestation). Only biochemical outcomes were reported.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Could not determine.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Free of baseline characteristic imbalance and we were not able to detect any other sources of bias</td>
</tr>
</tbody>
</table>

Yassa 2010

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial, set in a hospital and university department in the United States of America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Women with treated primary hypothyroidism seeking pregnancy, or newly pregnant at less than 11 weeks' gestation, with a normal baseline serum TSH (within 6 months of conception) and a stable dose of LT for at least 6 weeks were eligible. Participants with thyroid cancer were enrolled if TSH 0.1-2.5 mIU/litre. Participants without thyroid cancer were enrolled if TSH 0.5-5.0 mIU/litre. Women were only randomised once pregnant 60 women were enrolled and 48 successfully completed the protocol (10 women miscarried, 1 woman suffered a stillbirth and 1 other woman was diagnosed with a molar pregnancy)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Participants were assigned to 2 groups. Group A increased their pre-pregnancy LT doses by 2 additional tablets per week (9 total tablets per week; 29% increase). Group B increased their pre-pregnancy LT doses by 3 additional tablets per week (10 total tablets per week; 43% increase)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>TSH. Free T4. No clinical outcomes reported, although miscarriage and safety of intervention (adverse effects) were commented on</td>
</tr>
<tr>
<td>Notes</td>
<td>Participants had follow-up serum testing every 2nd week until 20 weeks' gestation and once more at 30 weeks. LT' dosage was adjusted 4 weekly (wk 4, 8, 12, 16, 20, 30) depending on TSH concentration and whether they had benign thyroid disease or thyroid</td>
</tr>
</tbody>
</table>
cancer. On the intervening weeks (wk 6, 10, 14, 18), LT dosage was modified only if TSH > 10 mIU/L or < 0.1 mIU/L.

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not detailed.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not detailed.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Not blinded.</td>
</tr>
<tr>
<td>Participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not detailed, however, considered unlikely to affect the objectively measured outcomes (i.e. serum TSH)</td>
</tr>
<tr>
<td>Clinician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not blinded, however, considered unlikely to affect the objectively measured outcomes (i.e. serum TSH)</td>
</tr>
<tr>
<td>Outcome Assessor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Analyses were performed on only the 48 women who completed the protocol. 10 women miscarried shortly after enrolment. 6 of the women had not been randomised, and therefore were not included in the study; 4 women who miscarried however had been randomised and had presented for initial testing, however, no further biochemical data were collected, and the women were not included in analyses. Another 2 women were excluded from analysis after randomisation - 1 woman suffered a stillbirth and the other was diagnosed with a molar pregnancy</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No clinical outcomes reported, only TSH concentrations. Miscarriages were presented in text, however it was unclear which group the women had been randomised to</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other obvious source of bias.</td>
</tr>
</tbody>
</table>
LT: levothyroxine  
mIU: million international units  
Se: selenomethionine  
TPOAb+: thyroid peroxidase antibody positive  
TPOAB-: thyroid peroxidase antibody negative  
TSH: thyroid stimulating hormone

**Characteristics of excluded studies [ordered by study ID]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 2002</td>
<td>Postpartum intervention: this randomised placebo controlled trial compared 100 μg of thyroxine versus placebo given daily to 446 TPOAb+ women from 6 weeks to 6 months postpartum, to stabilise thyroid function, and reduce the rate of occurrence and severity of associated depression</td>
</tr>
<tr>
<td>Lazarus 2012</td>
<td>This multi-centre randomised controlled trial recruited all women with singleton pregnancies before 16 weeks (i.e. including those with no history of thyroid disease). Women were allocated to a 'screen' group (thyroid function testing at randomisation, with thyroxine intervention if required) or ‘control’ group (thyroid function testing measured post delivery, with thyroxine intervention if required)</td>
</tr>
<tr>
<td>Negro 2010</td>
<td>This randomised trial included all pregnant women (i.e. including those with no history of thyroid disease) and allocated them during their first trimester to universal thyroid screening or to a control group. Women were stratified as high risk or low risk based on thyroid disease risks factors and if high risk, they were tested for free T4, TSH and thyroid peroxidase antibody and treated with levothyroxine if deemed to be hypo- or hyperthyroid</td>
</tr>
<tr>
<td>Petri 2011</td>
<td>This study was terminated prior to enrolment (<a href="http://clinicaltrials.gov/ct2/show/NCT01276782">http://clinicaltrials.gov/ct2/show/NCT01276782</a>). It was planned to be a pilot randomised controlled trial assessing thyroxine for autoimmune thyroid disease in systemic lupus erythematosus in pregnancy</td>
</tr>
</tbody>
</table>

free T3: unbound triiodothyronine  
free T4: unbound thyroxine  
TPOAb+: thyroid peroxidase antibody positive  
TSH: thyroid stimulating hormone

**Characteristics of ongoing studies [ordered by study ID]**

**Spong 2008**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>A randomised trial of thyroxine therapy for subclinical hypothyroidism or hypothyroxinaemia diagnosed during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised, double-blind, placebo-controlled trial. Participants will be screened for subclinical hypothyroidism or hypothyroxinaemia. Thyroid function tests will be performed monthly and the dosage adjusted based on test results. Children of these patients will have developmental testing done annually until they are five years of age</td>
</tr>
</tbody>
</table>
### Participants
Pregnant women less than 20 weeks' gestation.

### Interventions
Levothyroxine or placebo until delivery.

### Outcomes
**PRIMARY:** intellectual function of children at 5 years of age (Wechsler PreSchool and Primary Scale of Intelligence - WPPSI-III)
**SECONDARY:** developmental delay at 12 and 24 months (Bayley scales for MDI & PDI), attention deficit at 48 months (Connors Rating Scales and NEPSY attention subsets), behavioural problems and social competencies at 36 and 60 months of age (CBCL), fetal growth, preterm delivery, pre-eclampsia, abruption, stillbirth, development of postpartum thyroid dysfunction

### Starting date
October 2006.

### Contact information
Catherine Y Spong, MD
Tel: 301-435-6894, spongc@exchange.nih.gov

### Notes
Expected completion May 2014.
NCT00388297.

---

**CBCL:** Child Behaviour Checklist  
**MDI:** Mental Developmental Index  
**NEPSY:** NEuroPSYchological Assessment  
**PDI:** Psychomotor Development Index
DATA AND ANALYSES

Comparison 1. Levothyroxine versus no treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>1</td>
<td>105</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.61 [0.11, 3.48]</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1</td>
<td>105</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.28 [0.10, 0.80]</td>
</tr>
<tr>
<td>Miscarriage (first trimester)</td>
<td>1</td>
<td>115</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.25 [0.06, 1.15]</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1</td>
<td>105</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.65 [0.22, 1.92]</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>1</td>
<td>105</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.30 [0.01, 7.29]</td>
</tr>
</tbody>
</table>

Comparison 2. Selenomethionine versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>1</td>
<td>151</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.44 [0.25, 8.38]</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1</td>
<td>151</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.20, 4.61]</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>1</td>
<td>169</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.85 [0.30, 2.42]</td>
</tr>
<tr>
<td>Hypothyroidism (2 months after birth and after stopping levothyroxine)</td>
<td>1</td>
<td>151</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.77 [0.21, 2.75]</td>
</tr>
<tr>
<td>Postpartum thyroid dysfunction (within 12 months post delivery)</td>
<td>1</td>
<td>151</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.59 [0.38, 0.90]</td>
</tr>
<tr>
<td>Hypothyroidism (12 months post delivery)</td>
<td>1</td>
<td>151</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.58 [0.27, 1.24]</td>
</tr>
<tr>
<td>Thyroiditis (moderate or advanced at end of postpartum period)</td>
<td>1</td>
<td>151</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.61 [0.39, 0.95]</td>
</tr>
<tr>
<td>Thyroiditis (mild, moderate or advanced at end of postpartum period)</td>
<td>1</td>
<td>151</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.90, 1.12]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Levothyroxine versus no treatment, Outcome 1 Pre-eclampsia.

Review: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

Comparison: 1 Levothyroxine versus no treatment

Outcome: 1 Pre-eclampsia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Levothyroxine</th>
<th>No treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H Fixed, 95% CI</td>
<td></td>
<td>M-H Fixed, 95% CI</td>
</tr>
<tr>
<td>Negro 2006</td>
<td>2/55</td>
<td>3/50</td>
<td>100.0%</td>
<td>0.61 [0.11, 3.48]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>55</td>
<td>50</td>
<td>100.0%</td>
<td>0.61 [0.11, 3.48]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 2 (Levothyroxine), 3 (No treatment)
Heterogeneity: not applicable
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable

### Analysis 1.2. Comparison 1 Levothyroxine versus no treatment, Outcome 2 Preterm birth.

Review: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

Comparison: 1 Levothyroxine versus no treatment

Outcome: 2 Preterm birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Levothyroxine</th>
<th>No treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H Fixed, 95% CI</td>
<td></td>
<td>M-H Fixed, 95% CI</td>
</tr>
<tr>
<td>Negro 2006</td>
<td>4/55</td>
<td>13/50</td>
<td>100.0%</td>
<td>0.28 [0.10, 0.80]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>55</td>
<td>50</td>
<td>100.0%</td>
<td>0.28 [0.10, 0.80]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4 (Levothyroxine), 13 (No treatment)
Heterogeneity: not applicable
Test for overall effect: Z = 2.37 (P = 0.018)
Test for subgroup differences: Not applicable
### Analysis 1.3. Comparison 1 Levothyroxine versus no treatment, Outcome 3 Miscarriage (first trimester).

**Review:** Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy  
**Comparison:** 1 Levothyroxine versus no treatment  
**Outcome:** 3 Miscarriage (first trimester)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Levothyroxine n/N</th>
<th>No treatment n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negro 2006</td>
<td>2/57</td>
<td>8/58</td>
<td>0.25 [ 0.06, 1.15 ]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>57</td>
<td>58</td>
<td>0.25 [ 0.06, 1.15 ]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 2 (Levothyroxine), 8 (No treatment)  
Heterogeneity: not applicable  
Test for overall effect: Z = 1.78 (P = 0.075)  
Test for subgroup differences: Not applicable

### Analysis 1.4. Comparison 1 Levothyroxine versus no treatment, Outcome 4 Gestational hypertension.

**Review:** Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy  
**Comparison:** 1 Levothyroxine versus no treatment  
**Outcome:** 4 Gestational hypertension

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Levothyroxine n/N</th>
<th>No treatment n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negro 2006</td>
<td>5/55</td>
<td>7/50</td>
<td>0.65 [ 0.22, 1.92 ]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>55</td>
<td>50</td>
<td>0.65 [ 0.22, 1.92 ]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 (Levothyroxine), 7 (No treatment)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.78 (P = 0.43)  
Test for subgroup differences: Not applicable
### Analysis 1.5. Comparison 1 Levothyroxine versus no treatment, Outcome 5 Placental abruption.

**Review:** Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

**Comparison:** 1 Levothyroxine versus no treatment

**Outcome:** 5 Placental abruption

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Levothyroxine n/N</th>
<th>No treatment n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negro 2006</td>
<td>0/55</td>
<td>1/50</td>
<td></td>
<td>100.0%</td>
<td>0.30 [ 0.01, 7.29 ]</td>
</tr>
</tbody>
</table>

Total (95% CI) 55 50 100.0% 0.30 [ 0.01, 7.29 ]

Total events: 0 (Levothyroxine), 1 (No treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

### Analysis 2.1. Comparison 2 Selenomethionine versus placebo, Outcome 1 Pre-eclampsia.

**Review:** Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

**Comparison:** 2 Selenomethionine versus placebo

**Outcome:** 1 Pre-eclampsia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negro 2007</td>
<td>3/77</td>
<td>2/74</td>
<td></td>
<td>100.0%</td>
<td>1.44 [ 0.25, 8.38 ]</td>
</tr>
</tbody>
</table>

Total (95% CI) 77 74 100.0% 1.44 [ 0.25, 8.38 ]

Total events: 3 (Selenomethionine), 2 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable
Analysis 2.2. Comparison 2 Selenomethionine versus placebo, Outcome 2 Preterm birth.

Review: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

Comparison: 2 Selenomethionine versus placebo

Outcome: 2 Preterm birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Negro 2007</td>
<td>3/77</td>
<td>3/74</td>
<td>1.000 %</td>
<td>0.96 [0.20, 4.61]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>77</td>
<td>74</td>
<td>100.0 %</td>
<td>0.96 [0.20, 4.61]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 3 (Selenomethionine), 3 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Selenomethionine versus placebo, Outcome 3 Miscarriage.

Review: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

Comparison: 2 Selenomethionine versus placebo

Outcome: 3 Miscarriage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Negro 2007</td>
<td>6/85</td>
<td>7/84</td>
<td>1.000 %</td>
<td>0.85 [0.30, 2.42]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>85</td>
<td>84</td>
<td>100.0 %</td>
<td>0.85 [0.30, 2.42]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Selenomethionine), 7 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.31 (P = 0.76)
Test for subgroup differences: Not applicable
### Analysis 2.4. Comparison 2 Selenomethionine versus placebo, Outcome 4 Hypothyroidism (2 months after birth and after stopping levothyroxine).

**Review:** Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

**Comparison:** Selenomethionine versus placebo

**Outcome:** Hypothyroidism (2 months after birth and after stopping levothyroxine)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Negro 2007</td>
<td>4/77</td>
<td>5/74</td>
<td>100.0 %</td>
<td>0.77 [ 0.21, 2.75 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>77</strong></td>
<td><strong>74</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.77 [ 0.21, 2.75 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4 (Selenomethionine), 5 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

---

### Analysis 2.5. Comparison 2 Selenomethionine versus placebo, Outcome 5 Postpartum thyroid dysfunction (within 12 months post delivery).

**Review:** Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

**Comparison:** Selenomethionine versus placebo

**Outcome:** Postpartum thyroid dysfunction (within 12 months post delivery)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Negro 2007</td>
<td>22/77</td>
<td>36/74</td>
<td>100.0 %</td>
<td>0.59 [ 0.38, 0.90 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>77</strong></td>
<td><strong>74</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.59 [ 0.38, 0.90 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 22 (Selenomethionine), 36 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 2.46 (P = 0.014)

Test for subgroup differences: Not applicable
### Analysis 2.6. Comparison 2 Selenomethionine versus placebo, Outcome 6 Hypothyroidism (12 months post delivery).

Review: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

Comparison: 2 Selenomethionine versus placebo

Outcome: 6 Hypothyroidism (12 months post delivery)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Negro 2007</td>
<td>9/77</td>
<td>15/74</td>
<td>100.0 %</td>
<td>0.58 [ 0.27, 1.24 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>77</strong></td>
<td><strong>74</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.58 [ 0.27, 1.24 ]</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total events: 9 (Selenomethionine), 15 (Placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 1.42 (P = 0.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 2.7. Comparison 2 Selenomethionine versus placebo, Outcome 7 Thyroiditis (moderate or advanced at end of postpartum period).

Review: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

Comparison: 2 Selenomethionine versus placebo

Outcome: 7 Thyroiditis (moderate or advanced at end of postpartum period)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Negro 2007</td>
<td>21/77</td>
<td>33/74</td>
<td>100.0 %</td>
<td>0.61 [ 0.39, 0.95 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>77</strong></td>
<td><strong>74</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.61 [ 0.39, 0.95 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>
Analysis 2.8. Comparison 2 Selenomethionine versus placebo, Outcome 8 Thyroiditis (mild, moderate or advanced at end of postpartum period).

Review: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy

Comparison: 2 Selenomethionine versus placebo

Outcome: 8 Thyroiditis (mild, moderate or advanced at end of postpartum period)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selenomethionine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negro 2007</td>
<td>69/77</td>
<td>66/74</td>
<td>1.00 [0.90, 1.12]</td>
<td>100.0 %</td>
<td>1.00 [0.90, 1.12]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>77</td>
<td>74</td>
<td>100.0 %</td>
<td>1.00 [0.90, 1.12]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 69 (Selenomethionine), 66 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.08 (P = 0.93)
Test for subgroup differences: Not applicable

WHAT’S NEW

Last assessed as up-to-date: 8 April 2013.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 April 2013</td>
<td>New citation required but conclusions have not changed</td>
<td>One new trial included (Yassa 2010), conclusions not changed. Two new trials excluded (Negro 2010; Petri 2011). One previously ongoing study was also excluded (Lazarus 2012).</td>
</tr>
<tr>
<td>31 March 2013</td>
<td>New search has been performed</td>
<td>Search updated.</td>
</tr>
</tbody>
</table>

HISTORY

Protocol first published: Issue 2, 2009
Review first published: Issue 7, 2010
C O N T R I B U T I O N S O F A U T H O R S

For this update of the review, Sally Reid and Emily Bain assessed the eligibility and quality of the trials, performed data extraction and analyses, and drafted the review. Caroline Crowther, Philippa Middleton and Mary Cossich reviewed and commented on drafts.

For the previous version of the review, Sally Reid wrote the protocol and review with assistance from Caroline Crowther and Philippa Middleton. Sally Reid and Philippa Middleton assessed the eligibility and quality of the trials and performed data extraction and analyses. Sally Reid contacted authors of the papers for further information. Mary Cossich reviewed and commented on drafts.

D E C L A R A T I O N S O F I N T E R E S T

None known.

S O U R C E S O F S U P P O R T

Internal sources

- ARCH, Robinson Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

External sources

- National Health and Medical Council, Australia.
- Department of Health and Ageing, Australia.

D I F F E R E N C E S B E T W E E N P R O T O C O L A N D R E V I E W

In this review update, we clarified that studies published as abstracts only would be included, and the methods were updated to reflect current methods of the Pregnancy and Childbirth Group.

We included the secondary outcome 'Death' (defined as all fetal or neonatal deaths) as this was considered important for this review question, along with the outcome 'Neonatal death' alone. We included 'Miscarriage' under the outcome 'Fetal death'.

We clarified in the methods, that trials comparing interventions for hypothyroidism and/or subclinical hypothyroidism pre-pregnancy and/or during pregnancy with another intervention or placebo are eligible for inclusion. We have also added 'prepregnancy' to the review's title for further clarification.

In the previous version of the review, the outcome measure 'thyroiditis' was added to the review as it was thought to be important. The outcome definitions for postpartum haemorrhage and postpartum depression were also altered to accommodate more data.
INDEX TERMS

Medical Subject Headings (MeSH)
Abortion, Spontaneous [prevention & control]; Hormone Replacement Therapy; Hypothyroidism [*drug therapy]; Pre-Eclampsia [prevention & control]; Preconception Care [methods]; Pregnancy Complications [*drug therapy]; Pregnancy Outcome; Premature Birth [prevention & control]; Randomized Controlled Trials as Topic; Selenomethionine [*therapeutic use]; Thyroid Gland [immunology]; Thyroiditis, Autoimmune [drug therapy]; Thyroxine [*therapeutic use]

MeSH check words
Female; Humans; Pregnancy