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Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism (Review)

Akhtar MA, Agrawal R, Brown J, Sajjad Y, Craciunas L

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Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism.
Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD011009.
DOI: 10.1002/14651858.CD011009.pub2.

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[Intervention Review]

Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New, published in Issue 6, 2019.

Citation: Akhtar MA, Agrawal R, Brown J, Sajjad Y, Craciunas L. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. *Cochrane Database of Systematic Reviews* 2019, Issue 6. Art. No.: CD011009. DOI: 10.1002/14651858.CD011009.pub2.

ABSTRACT

Background

Thyroid disease is the second most common endocrine disorder affecting women of reproductive age. Subclinical hypothyroidism is diagnosed by an elevated thyroid-stimulating hormone concentration with a normal concentration of free thyroxine hormone. Autoimmune thyroid disease (ATD) is diagnosed by the presence of thyroid autoantibodies, regardless of thyroid hormone levels. Thyroxine may be a useful treatment for subfertile women with these two specific types of thyroid disease for improving pregnancy outcomes during assisted reproduction.

Objectives

To evaluate the efficacy and harms of levothyroxine replacement in subfertile women with subclinical hypothyroidism or with normal thyroid function and thyroid autoimmunity (euthyroid autoimmune thyroid disease, or euthyroid ATD) undergoing assisted reproduction.

Search methods

We searched the Cochrane Gynaecology and Fertility (CGF) Group specialised register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL and two trials registers together with reference checking and contact with study authors and experts in the field to identify studies. We searched for all published and unpublished randomised controlled trials (RCTs) comparing thyroxine with no treatment or placebo, without language restrictions, from inception to 8 April 2019, and in consultation with the Cochrane CGF Information Specialist.

Selection criteria

We included women undergoing assisted reproduction treatment, meaning both in vitro fertilisation and intracytoplasmic sperm injection, with a history of subfertility and with subclinical hypothyroidism or with euthyroid ATD. We excluded women with a previously known clinical hypothyroidism or already taking thyroxine or tri-iodothyronine. RCTs compared thyroxine (levothyroxine) with either placebo or no treatment.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary review outcomes were live birth and adverse events of thyroxine; our secondary outcomes were clinical pregnancy, multiple pregnancy and miscarriage.

Main results

The review included four studies with 820 women. The included studies were of overall low risk of bias. Using GRADE methodology, we assessed the quality of evidence for the primary outcomes of this review to be very low- to low-quality evidence. Evidence was downgraded for imprecision as it was based on single, small trials with wide confidence intervals (CI). We were able to include data from three of the four included studies.

In one study of women with both subclinical hypothyroidism and positive or negative anti-TPO antibodies (autoimmune disease), the evidence suggested that thyroxine replacement may have improved live birth rate (RR 2.13, 95% CI 1.07 to 4.21; 1 RCT, n = 64; low-quality evidence) and it may have led to similar miscarriage rates (RR 0.11, 95% CI 0.01 to 1.98; 1 RCT, n = 64; low-quality evidence). The evidence suggested that women with both subclinical hypothyroidism and positive or negative anti-TPO antibodies would have a 25% chance of a live birth with placebo or no treatment, and that the chance of a live birth in these women using thyroxine would be between 27% and 100%.

In women with normal thyroid function and thyroid autoimmunity (euthyroid ATD), treatment with thyroxine replacement compared with placebo or no treatment may have led to similar live birth rates (risk ratio (RR) 1.04, 95% CI 0.83 to 1.29; 2 RCTs, number of participants (n) = 686; I^2 = 46%; low-quality evidence) and miscarriage rates (RR 0.83, 95% CI 0.47 to 1.46, 2 RCTs, n = 686, I^2 = 0%; low-quality evidence). The evidence suggested that women with normal thyroid function and thyroid autoimmunity would have a 31% chance of a live birth with placebo or no treatment, and that the chance of a live birth in these women using thyroxine would be between 26% and 40%.

Adverse events were rarely reported. One RCT reported 0/32 in the thyroxine replacement group and 1/32 preterm births in the control group in women diagnosed with subclinical hypothyroidism and positive or negative anti-TPO antibodies. One RCT reported 21/300 preterm births in the thyroxine replacement group and 19/300 preterm births in the control group in women diagnosed with positive anti-TPO antibodies. None of the RCTs reported on other maternal pregnancy complications, foetal complications or adverse effects of thyroxine.

Authors' conclusions

We could draw no clear conclusions in this systematic review due to the very low to low quality of the evidence reported.

PLAIN LANGUAGE SUMMARY

Thyroxine replacement therapy for subfertile women with autoimmune thyroid disease or mildly underactive thyroid

Review question

Does hormone supplementation with thyroxine (levothyroxine) improve fertility outcomes after in vitro fertilisation (a fertility treatment where an egg is combined with sperm outside the body) or intracytoplasmic sperm injection (a fertility treatment where a single sperm is injected directly into an egg) for women diagnosed with presence of thyroid antibodies (autoimmune thyroid disease; ATD) or mildly underactive thyroid?

Background

Thyroid disease is the second most common hormonal disorder affecting women of reproductive age. Research has shown a higher rate of miscarriage and reduced fertility in women with underactive (slow-working) thyroid, with both thyroid hormones measured in blood testing being low. However, there is also a mild variant of this thyroid disease, the so-called 'subclinical' or mildly underactive thyroid in which affected people show no symptoms and only have a mild change in one of the thyroid hormones when testing blood levels. Another mild variant of thyroid disease is the so-called 'ATD,' with normal thyroid hormone levels, but the presence of thyroid antibodies. Antibodies could attack a woman's own body cells, and the presence of thyroid antibodies is associated with a higher risk of miscarriage. To date, it is unclear what these mild subtypes of thyroid disease do to female fertility and pregnancy outcomes.

Study characteristics

Cochrane authors performed a comprehensive literature search of the standard medical databases to 8 April 2019 in consultation with the Cochrane Gynaecology and Fertility Group Information Specialist, for randomised clinical trials (RCTs: clinical studies where people are randomly put into one of two or more treatment groups) investigating the effect of thyroid hormones (levothyroxine) for women diagnosed with ATD or mildly underactive thyroid who were planning to undergo assisted reproduction. Two authors independently selected studies, evaluated them, extracted data and attempted to contact the authors where data were missing.

We found four RCTs (with 820 women) that met our inclusion requirements. The thyroid hormones were administered in a range of doses to women diagnosed with mildly underactive thyroid or presence of thyroid antibodies (ATD).

Key results

In women with mild thyroid hormone imbalance and unknown thyroid autoimmunity status, we were uncertain whether thyroxine replacement had an effect on live birth or miscarriage rates (very low-quality evidence from one study involving 70 women).

In women with mildly underactive thyroids (with or without ATD), the evidence suggested that thyroxine replacement may have improved live birth rates (low-quality evidence from one study involving 64 women) and it may have led to similar miscarriage rates (low-quality evidence from one study involving 64 women). The evidence suggested that women with mildly underactive thyroid (with or without ATD) would have a 25% chance of a live birth with placebo or no treatment, and 27% to 100% with thyroxine.

In women with ATD and normal thyroid function, treatment with thyroxine replacement compared with placebo or no treatment may have led to similar live birth rates (low-quality evidence from two studies involving 686 women) and miscarriage rates (low quality evidence from two studies involving 686 women). The evidence suggested that women with ATD and normal thyroid function would have a 31% chance of a live birth with placebo or no treatment, and 26% to 40% with thyroxine.

Side effects were rarely reported. One study reported none out of 32 preterm births in the thyroxine replacement group and one out of 32 preterm births in the control group in women diagnosed with mildly underactive thyroid (with or without ATD). One study reported 21 out of 300 preterm births in the thyroxine replacement group and 19 out of 300 preterm births in the control group in women diagnosed with ATD and normal thyroid function. None of the studies reported on other maternal pregnancy complications, foetal complications or side effects of thyroxine.

Quality of the evidence

The evidence was of very low to low quality. We downgraded the evidence as it was based on single, small trials with widely variable results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Thyroxine compared to placebo or no treatment for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism

Thyroxine compared to placebo or no treatment for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism

Patient or population: subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism

Setting: assisted reproduction units

Intervention: thyroxine (levothyroxine)

Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or no treatment	Risk with thyroxine			
Live birth rate – euthyroid women with anti-TPO antibodies Follow-up: mean 40 weeks	312 per 1000	324 per 1000 (259 to 402)	**RR 1.04** (0.83 to 1.29)	686 (2 RCTs)	⊕⊕⊖⊖ **Low**[a]
Live birth rate – subclinical hypothyroidism with or without anti-TPO antibodies Follow-up: mean 40 weeks	250 per 1000	533 per 1000 (268 to 1000)	**RR 2.13** (1.07 to 4.21)	64 (1 RCT)	⊕⊕⊖⊖ **Low**[c]
Adverse events including maternal pregnancy complications, foetal complications and adverse effects of thyroxine	1 RCT reported 0/32 preterm births in the experimental group and 1/32 preterm births in the control group in women diagnosed with subclinical hypothyroidism and positive or negative anti-TPO antibodies. 1 RCT reported 21/300) preterm births in the experimental group and 19/300 preterm births in the control group in women diagnosed with positive anti-TPO antibodies. None of the RCTs reported on other adverse events.				
Miscarriage – anti-TPO antibodies Follow-up: mean 40 weeks	67 per 1000	56 per 1000 (32 to 98)	**RR 0.83** (0.47 to 1.46)	686 (2 RCTs)	⊕⊕⊖⊖ **Low**[a]
Miscarriage – subclinical hypothyroidism with or without anti-TPO antibodies Follow-up: mean 40 weeks	125 per 1000	14 per 1000 (1 to 248)	**RR 0.11** (0.01 to 1.98)	64 (1 RCT)	⊕⊕⊖⊖ **Low**[c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Anti-TPO: anti-thyroid peroxidase; **CI:** confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded two levels for very serious imprecision: only two studies with fewer than 300 events, broad confidence intervals.
[b]Downgraded one level for incorrect reporting of statistical testing and results (inconsistent) in the original publication.
[c]Downgraded two levels for very serious imprecision: only one study with fewer than 30 events, very broad confidence intervals.

BACKGROUND

Description of the condition

Thyroid disease is the second most common endocrine disorder affecting women of reproductive age (Carney 2014). Symptoms of hypothyroidism include fatigue, intolerance of cold, weight gain, constipation, dry skin and muscle cramps (Reid 2010). Thyroid hormones affect carbohydrate, fat, protein, and vitamin metabolism and energy production thereby enabling body organs to function effectively. Hypothyroidism may cause menstrual abnormalities such as anovulation, oligomenorrhoea and by interfering with the hypothalamic–pituitary–gonadal axis and the peripheral metabolism of sex steroids (Poppe 2003). Women diagnosed with hypothyroidism are at higher risk of obstetric complications such as miscarriage and adverse neonatal outcomes (Poppe 2003).

Thyroid hormones have diverse effects on ovarian function. They may be important for ovarian follicle development and maturation of the cumulus–oocyte complex. Several isoforms of thyroid hormone receptor messenger ribonucleic acid (mRNA) are expressed in the human oocyte. Hence, thyroid hormones may have direct and indirect effects on the oocyte, as well as on the granulosa and cumulus cells (Zhang 1997). Hypothyroidism can thus disrupt normal ovarian function (Van Voorhis 1994).

Thyroid hormone receptors have been described in human oocytes, where they synergise with the luteinising hormone and human chorionic gonadotrophin (hCG) receptor, mediated by follicle-stimulating hormone, to exert direct stimulatory effects on granulosa cell function (that is, progesterone production) and on trophoblastic differentiation (Poppe 2008).

Thyroxine circulates in the blood bound to thyroxine-binding globulin (TBG) and only free, unbound thyroxine is available to tissues. TBG production by the liver, similar to other binding proteins, rises in states of high circulating oestradiol concentrations such as the pregnant state (Glinoer 1977a; Glinoer 1977b).

Clinical hypothyroidism

Clinical hypothyroidism is defined as symptomatic thyroid hormone deficiency. It is diagnosed by an elevated thyroid-stimulating hormone (TSH) concentration with a low concentration of free thyroxine hormone (FT4). If TSH is elevated, measurement of FT4 is needed to confirm the presence of clinical hypothyroidism. Clinical hypothyroidism occurs in 2% to 3% of women of child-bearing age (Jameson 2011), and thyroxine replacement is routinely prescribed to correct the thyroid hormone deficiency. Clinical hypothyroidism is not part of the scope of this review.

Subclinical hypothyroidism

Subclinical hypothyroidism is defined as biochemical evidence of thyroid hormone deficiency in women with few or no apparent symptoms. It is diagnosed by an elevated TSH concentration with a normal concentration of FT4. Subclinical hypothyroidism is observed in 6% to 8% of women of child-bearing age (and 10% in women over the age of 60 years) (Vissenberg 2015). The annual risk of progressing from subclinical to clinical hypothyroidism is 4% when antithyroid peroxidase (anti-TPO) antibodies are also present (Jameson 2011).

Euthyroid autoimmune thyroid disease

Women with euthyroid autoimmune thyroid disease (ATD) have normal TSH and FT4 concentrations with the presence of thyroid autoantibodies. ATD is detected by measuring the concentrations of anti-TPO antibodies and thyroglobulin (Tg) antibodies. Almost all people with ATD have high concentrations of anti-TPO antibodies. However, the occurrence of Tg antibodies alone is relatively uncommon. Anti-TPO antibodies are most routinely tested. ATD may be associated with goitre (Hashimoto's thyroiditis) or, at the later stages of the disease, minimal residual thyroid tissue (atrophic thyroiditis) (Jameson 2011). Thyroid dysfunction is more frequent in women with positive anti-TPO antibodies titres and this may interfere with normal ovarian function (Poppe 2008).

The susceptibility to ATD is determined by a combination of genetic and environmental factors (Iddah 2013). Transplacental passage of Tg or anti-TPO antibodies has no effect on the foetal thyroid, which suggests that ATD is T cell-mediated autoimmunity (Kim 2011b).

ATD affects 5% to 20% of women of child-bearing age (Artini 2013; Krassas 2010). ATD is more prevalent in infertile women (Artini 2013; Krassas 2010; Kim 2011b; Poppe 2008; Trokoudes 2006; Van den Boogaard 2011), and has been associated with an increased miscarriage rate after spontaneous conception (Artini 2013; Kim 2011b; Poppe 2008; Trokoudes 2006; Van den Boogaard 2011), and in subfertile women achieving pregnancy by assisted reproduction treatment (ART) (Toulis 2010). Oocyte fertilisation and pregnancy rates were lower while miscarriage rates were higher in women with ATD undergoing ART. There was a significant presence of thyroid autoantibodies (anti-TPO, Tg) in the follicular fluid of all women with ATD and the concentrations of anti-TPO and Tg antibodies positively correlated with serum concentrations (Monteleone 2011). A higher prevalence of ATD is also reported in subfertile women with endometriosis (Artini 2013; Poppe 2008; Trokoudes 2006), and polycystic ovarian syndrome (PCOS) (Janssen 2004; Poppe 2008). There is also a significant positive correlation between the presence of ATD and premature ovarian failure (Abalovich 2007). ATD is associated with impaired cellular and humoral immune responses including an increase in the natural killer (NK) cell concentrations in women with unexplained infertility, although there were no significant differences in NK cytotoxic activity (Kim 2011b). It is suggested that the presence of thyroid antibodies and an elevated TSH concentration increase interleukin 2 (IL-2) production causing IL-2-mediated NK cell activation, thus leading to reproductive failures and miscarriages (Konova 2010).

Description of the intervention

The intervention investigated by the present review was thyroxine/levothyroxine replacement in women undergoing ART following a diagnosis of subclinical hypothyroidism or ATD, or both. There was no consensus regarding the dosage, timing and follow-up of thyroxine replacement during ART for subfertile women with subclinical hypothyroidism or euthyroid women with ATD.

Controlled ovarian hyperstimulation (COH) during ART cycles involves downregulation of the pituitary–gonadal axis by using gonadotrophin-releasing hormone (GnRH) analogues and then triggering final oocyte maturation with hCG. COH induces an increase in oestradiol (E2) concentrations resulting in excess TBG production by the liver, which leads to an increase in

circulating thyroxine-binding sites. This causes a reduction in FT4 concentrations thus resulting in a compensatory increase in TSH production from the pituitary gland (Mintziori 2011).

TSH and hCG share structural homologies and receptors. This results in endogenous hCG having thyrotropic effects (Haddow 2008). High hCG concentrations during COH may be associated with thyroid stimulation of function (lower serum TSH concentrations) and anatomically an increased thyroid volume (Mintziori 2011).

A significant elevation in TSH concentrations has been reported in women who have COH during ART (Gracia 2012). Therefore, euthyroid women with ATD before pregnancy may develop overt hypothyroidism during ART cycles, with or without resulting pregnancy, as a result of these hormonal changes (Kim 2011b; Poppe 2004).

COH leads to a significant increase in circulating E2 concentration, which in turn may have an adverse effect on thyroid hormones and TSH. In the presence of ATD, the impact of COH on thyroid dysfunction may become more severe (Krassas 2010; Muller 2000).

How the intervention might work

The goal of thyroxine replacement is to normalise serum TSH concentrations (De Groot 2012; Stagnaro-Green 2011). Replacement with levothyroxine to normalise TSH concentrations is a well-known intervention for hypothyroidism in an iodine-sufficient population (Reid 2010).

Women with ATD treated with thyroid replacement therapy had a lower risk of miscarriage compared with a similar group treated with intravenous immunoglobulin (Trokoudes 2006). Babies born to women undergoing ART with a preconception TSH concentration greater than 2.5 mIU/L had a lower gestational age at delivery and a lower birth weight (Baker 2006).

The US National Center on Birth Defects and Developmental Disability of the Centres for Disease Control and Prevention (CDC) and the American Thyroid Association recommended that euthyroid woman with known ATD prior to conception should have a serum TSH concentration assessed and levothyroxine therapy initiated if the serum TSH concentration is greater than 2.5 mIU/L prior to pregnancy, for all women not known to have overt clinical hypothyroidism (Mandel 2005). The American Thyroid Association published guidelines in 2011 and have advised that there is insufficient evidence to recommend universal levothyroxine replacement in all pregnant women with subclinical hypothyroidism; however, if they have subclinical hypothyroidism with presence of thyroid antibodies, then the women should be treated with levothyroxine replacement (Stagnaro-Green 2011).

The Endocrine Society clinical practice guidelines recommend screening all women over the age of 30 years or all infertile women seeking pregnancy, or both, for targeted thyroid disease case finding (De Groot 2012). Women with the presence of thyroid antibodies in their circulation are at increased risk of miscarriage, preterm delivery, progression of hypothyroidism and postpartum thyroiditis. Therefore, if identified, such women should be screened for serum TSH abnormalities before pregnancy. If serum TSH is over 2.5 mIU/L at the time of testing, then levothyroxine therapy should be initiated. The Endocrine Society also recommends levothyroxine replacement in women with subclinical hypothyroidism with or without the presence of thyroid antibodies and, if already treated, that a prepregnancy TSH concentration should not be in excess of 2.5 mIU/L (De Groot 2012).

Why it is important to do this review

The menstrual pattern is influenced by thyroid hormones, directly through an effect on the ovaries and indirectly through an impact on sex hormone-binding globulin, prolactin, GnRH secretion and coagulation factors. Serum TSH concentrations are a significant predictor of fertilisation failure in women undergoing in vitro fertilisation (IVF), supporting the importance of the role of thyroid hormones in oocyte physiology. Cramer and colleagues in their prospective study reported that TSH concentrations were significantly higher among women who produced oocytes that failed to fertilise (Cramer 2003). Among women who had at least one oocyte inseminated, the likelihood that they would have less than 50% of their eggs fertilised was significantly related to higher TSH concentrations in one multivariate model. Therefore, it was concluded that TSH may predict poor fertilisation rates in IVF and this reflects the importance of thyroid hormones in oocyte physiology (Cramer 2003).

Further, two meta-analyses reported an association between the presence of thyroid antibodies and miscarriage in subfertile women in cohort and case-control studies (Thangaratinam 2011), and in longitudinal studies involving populations of unselected women (Prummel 2004). It has also been reported by case-control studies that levothyroxine replacement is helpful in reducing miscarriage in populations of unselected women with normal thyroid function and thyroid autoantibodies (risk ratio (RR) 0.48, 95% confidence interval (CI) 0.25 to 0.92; P = 0.03) (Thangaratinam 2011).

The presence of ATD is associated with a significantly higher risk of miscarriage in women who become pregnant following ART, but it has no effect on the pregnancy rate. Therefore, determining the presence of ATD before embryo transfer may be useful in identifying women at risk of miscarriage.

The aim of this review was to provide fertility experts and consumers with evidence-based knowledge about the efficacy of thyroxine replacement in terms of improving clinical pregnancy and live birth rates in subfertile women with subclinical hypothyroidism or euthyroid ATD during ART. In this review, we did not assess the efficacy of thyroxine on the outcome of natural conceptions.

OBJECTIVES

To evaluate the efficacy and harms of levothyroxine replacement in subfertile women with subclinical hypothyroidism or with euthyroid ATD undergoing assisted reproduction.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and cross-over trials (using only data from the first phase for meta-analysis).

We excluded quasi-randomised trials.

Types of participants

Inclusion criteria:

- women undergoing ART, IVF or intracytoplasmic sperm injection (ICSI), for subfertility following a diagnosis of subclinical hypothyroidism or euthyroid ATD, or both.

Exclusion criteria:

- women having stimulated and unstimulated intrauterine insemination (IUI) or natural conception;
- women with previously known clinical hypothyroidism or already taking thyroxine or tri-iodothyronine.

Types of interventions

Thyroxine at any dosage or duration compared with no treatment or placebo.

Types of outcome measures

Primary outcomes

- Live birth rate per woman randomised (live birth was defined by *The International Glossary on Infertility and Fertility Care* as the birth of a baby after 22 completed weeks of gestational age as long as it showed signs of life) (Zegers-Hochschild 2017).
- Adverse events: including direct adverse effects of thyroxine (e.g. allergic reactions, hyperthyroidism), maternal pregnancy complications (e.g. preterm delivery, pre-eclampsia (preterm delivery defined as delivery of foetus after 22 weeks' and before 37 weeks' gestation)), and foetal complications during pregnancy (e.g. intrauterine growth restriction).

Secondary outcomes

- Clinical pregnancy rate per woman randomised (clinical pregnancy diagnosed by ultrasound or by the presence of clinical signs of pregnancy).
- Multiple pregnancy rate per woman randomised and per total number of pregnancies (multiple pregnancy diagnosed by ultrasound).
- Miscarriage rate per woman randomised and per pregnancy with per woman data prioritised (miscarriage defined as the spontaneous loss of an intrauterine pregnancy prior to 22 completed weeks of pregnancy).

Search methods for identification of studies

We searched for all published and unpublished RCTs comparing thyroxine with no treatment or placebo, without language restriction, from database inception to 8 April 2019, and in consultation with the Cochrane Gynaecology and Fertility Group (CGF) Information Specialist.

Electronic searches

We searched the following electronic databases, trial registers and websites:

- the Cochrane Gynaecology and Fertility Specialised Register of controlled trials (searched 8 April 2019, PROCITE platform) (Appendix 1);
- Cochrane Central Register of Studies Online (CENTRAL CRSO) (searched 8 April 2019, web platform) (Appendix 2);
- MEDLINE (searched from 1946 to 8 April 2019, Ovid platform) (Appendix 3);
- Embase (searched from 1980 to 8 April 20198, Ovid platform) (Appendix 4);
- PsycINFO (searched from 1806 to 8 April 2019, Ovid platform) (Appendix 5);
- CINAHL (searched from 1961 to 8 April 2019, EBSCO platform) (Appendix 6).

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying RCTs which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 6.4.11; Higgins 2011). The Embase, PsycINFO and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN; www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials included:

- trial registers for ongoing and registered trials
  - ClinicalTrials.gov (www.clinicaltrials.gov; a service of the US National Institutes of Health)'
  - the World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx);
- DARE (Database of Abstracts of Reviews of Effects) in the Cochrane Library (onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html; for reference lists from relevant non-Cochrane reviews);
- the Web of Knowledge (wokinfo.com/; a source of trials and conference abstracts);
- OpenGrey (www.opengrey.eu/; for unpublished literature from Europe);
- LILACS database (regional.bvsalud.org/php/index.php?lang=en;);
- Google (for recent trials not yet indexed in MEDLINE).

Searching other resources

We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. We also handsearched relevant journals and conference abstracts that are not covered in the CGF register, in liaison with the Information Specialist.

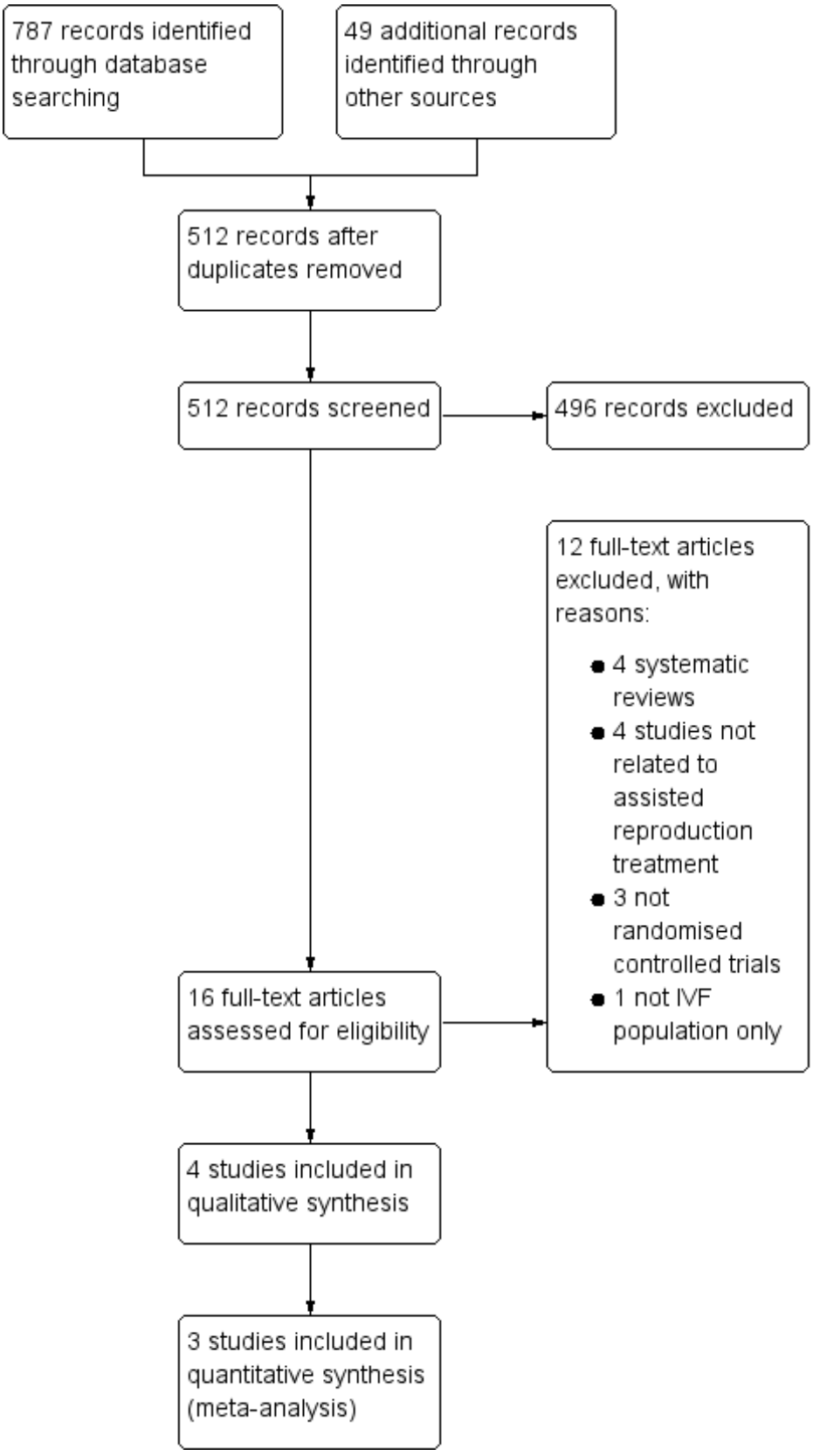
Data collection and analysis

We performed statistical analysis in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We entered data into Review Manager 5 (Review Manager 2014), and assessed evidence quality using GRADE methods.

Selection of studies

A PRISMA flow chart documented the selection process (Figure 1).

Figure 1. Study flow diagram.



Two review authors (MA and LC) independently scrutinised the title, abstract and keywords of every record retrieved to determine which studies required further assessment. We retrieved the full texts when the information suggested that the RCT intervention was thyroxine as an adjunct to ART.

If there were any doubts regarding these criteria from scanning the titles and abstracts, we obtained the full article for clarification. A third review author resolved disagreements by discussion where necessary. We contacted the authors of trials to request missing data.

Data extraction and management

Two review authors (MA and LC) independently extracted data from the included studies using a data extraction form designed and piloted by the authors. Where a trial had multiple publications, we used the main trial report as the primary source of evidence supplemented by additional material from the secondary publications. We checked to ensure that data were not used twice within analyses. We attempted to correspond with authors of original papers where there were any missing data or lack of clarity. We planned to refer any disagreements to a third review author (RA).

Assessment of risk of bias in included studies

Two review authors (MA and LC) independently performed assessment of risk of bias in the included studies. The review authors specifically assessed the quality of allocation (random sequence generation and allocation concealment), blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias. We described all judgements fully and presented them in the 'Risk of bias' table using the criteria specified by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to refer any disagreements to a third review author (RA).

Measures of treatment effect

For dichotomous outcomes (e.g. adverse events), we recorded the number of participants experiencing the event in each group of the trial. We calculated the risk ratio (RR) and 95% confidence intervals (CI) for all outcomes. None of the outcomes proposed were continuous variables.

Unit of analysis issues

The primary analysis was per woman randomised. There were no data per cycle reported. If reported, this would have been briefly summarised in an additional table. We planned to count multiple live births (e.g. twins or triplets) as one live birth event. We included only first-phase data from cross-over trials.

Dealing with missing data

Analysis was by the intention-to-treat principle where possible. We contacted the authors of the RCTs to source any missing data or to resolve any queries.

Where included studies did not report the primary outcome of live birth but did report on interim measures such as clinical pregnancy rates, we planned to undertake informal assessment as to whether these interim values were similar to those reported in the trials that did report live birth.

Assessment of heterogeneity

The review authors checked to see if the participants, interventions and outcomes in the included studies were similar enough to consider pooling in a meta-analysis.

We tested for heterogeneity using the Chi^2 test, with significance set at P less than 0.1. We used the I^2 statistic to estimate the total variation across studies that was due to heterogeneity, where less than 25% was considered as low heterogeneity, 25% to 50% as moderate and greater than 50% as high heterogeneity. If there were high levels of heterogeneity (I^2 greater than 50%) for the primary outcomes, we explored possible sources of heterogeneity using the subgroup and sensitivity analyses described below (Subgroup analysis and investigation of heterogeneity; Sensitivity analysis), in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

We were vigilant for duplication of publications. To assess for publication bias, we planned to produce a funnel plot where there were 10 or more trials reporting on an outcome, or we would have used other corrective analytical methods depending on the number of included studies (Egger 1997).

Data synthesis

We combined data in a meta-analysis if sufficient studies were available for inclusion. We used Review Manager 5 to perform the meta-analyses with a fixed-effect model to calculate pooled RR and 95% CI (Review Manager 2014). To aid interpretation, we translated findings for primary outcomes to absolute risks, expressed as percentages based on the 95% CIs.

We combined data from primary studies in the following comparison:

- thyroxine versus no treatment or placebo.

An increase in the risk of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), was displayed graphically in the forest plot to the right of the centre line and a decrease in the risk of an outcome to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

Where data were available (at least three contributing studies), we planned to conduct subgroup analyses to determine the separate evidence within the following subgroups:

- different ART methods (IVF versus ICSI, fresh versus frozen embryo transfer);
- duration and dosage of thyroxine during ART.

Women with subclinical hypothyroidism and euthyroid women with ATD were considered different populations.

Factors such as length of follow-up and adjusted or unadjusted analysis were considered in the interpretation of any heterogeneity.

Sensitivity analysis

We performed sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility of studies and analysis.

These sensitivity analyses included consideration of whether the review conclusions would have differed if:

- eligibility was restricted to studies without high risk of bias, defined as studies at low risk of selection bias and not at high risk of bias in any domain;
- a random-effects model had been adopted;
- the summary effect measure was odds ratio rather than RR.

Overall quality of the body of evidence: 'Summary of findings' table

We presented a Summary of findings for the main comparison using GRADEpro GDT 2015. This table evaluated the overall quality of the body of evidence for the primary review outcomes (live birth rate and adverse events) and secondary outcome of miscarriage for the main review comparison (levothyroxine versus placebo or no treatment). We assessed the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias). Two review authors independently judged quality of evidence (high, moderate, low or very low) and resolved disagreements by discussion. We justified, documented and incorporated judgements for each outcome. We extracted study data, formatted our comparisons in data tables and prepared the 'Summary of findings' table before writing the results and conclusions of our review.

RESULTS

Description of studies

Results of the search

The last systematic search was 8 April 2019 and identified 836 publications (787 from databases, 49 from other sources). Sixteen publications were potentially relevant and we assessed these in full text. Four publications met the inclusion criteria and were included in this review (Abdel Rahman 2010; Kim 2011a; Negro 2005; Wang 2017). See Figure 1 for detailed search results.

Included studies

Study design and setting

All four included studies were parallel-arm RCTs. They were published in full text and one reported external sources of funding (non-commercial) (Wang 2017). Studies were conducted in Egypt (Abdel Rahman 2010), South Korea (Kim 2011a), Italy (Negro 2005), and China (Wang 2017). The studies were conducted between 2006 and 2007 (Abdel Rahman 2010), 2006 and 2009 (Kim 2011a), 1999 and 2003 (Negro 2005), and 2012 and 2016 (Wang 2017).

Participants

Participants were women/couples undergoing ART for different causes of subfertility. The four studies included different populations from the thyroid disease point of view: Negro 2005 included 86 women and Wang 2017 included 600 women diagnosed with anti-TPO antibodies, Abdel Rahman 2010 included 70 women diagnosed with subclinical hypothyroidism and unknown thyroid autoimmunity status, while Kim 2011a included 64 women diagnosed with subclinical hypothyroidism out of which 51 were positive for anti-TPO antibodies.

Interventions and comparators

The experimental arms differed between the four included studies. Negro 2005 treated women with levothyroxine 1 µg/kg/day starting one month prior to ART and continued throughout the pregnancy. Abdel Rahman 2010 treated women with a variable dose of levothyroxine aiming at normalising the TSH level one month prior to ART and continued throughout the pregnancy. Kim 2011a treated women with levothyroxine 50 µg starting on the day of ovarian hyperstimulation and continued throughout the pregnancy aiming for a TSH concentration of less than 2.5 mIU/L. Wang 2017 treated women with variable doses of levothyroxine: 25 µg (if TSH less than 2.5 mIU/L) or 50 µg (if TSH greater than 2.5 mIU/L) aiming to keep the TSH concentrations within 0.1 mIU/L to 2.5 mIU/L in the first trimester, 0.2 mIU/L to 3.0 mIU/L in the second trimester and 0.3 mIU/L to 3.0 mIU/L in the third trimester.

Both Abdel Rahman 2010 and Negro 2005 compared the intervention with placebo, while Kim 2011a and Wang 2017 used no treatment but administered levothyroxine if there was clinical hypothyroidism diagnosed at any point in the pregnancy.

Outcomes

All four included studies reported on clinical pregnancy, miscarriage and live birth. Kim 2011a and Wang 2017 reported on preterm birth, while Wang 2017 reported on multiple pregnancy. No studies reported on maternal and other foetal complications or adverse effects of levothyroxine.

The data for Abdel Rahman 2010 are from an initial publication, giving results in percentages, and a published correction with absolute numbers. The data were inconsistent and we were unable to clarify details although we made several unsuccessful attempts to contact the study authors. On advice from CGF editors we have not included this study in our analyses.

Excluded studies

We excluded 12 studies: systematic reviews (Busnelli 2016; Mintziori 2016; Rao 2018; Velkeniers 2013), not answering the PICO (Population, Intervention, Comparison, Outcome) question (Blumenthal 2017; Dhillon-Smith 2019, Maraka 2016; Nazarpour 2017; Negro 2006), and not being an RCT (De Brucker 2016; Mumuşoğlu 2016; Riestenberg 2016).

Risk of bias in included studies

Refer to Figure 2; Figure 3 for details of risk of bias judgements.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

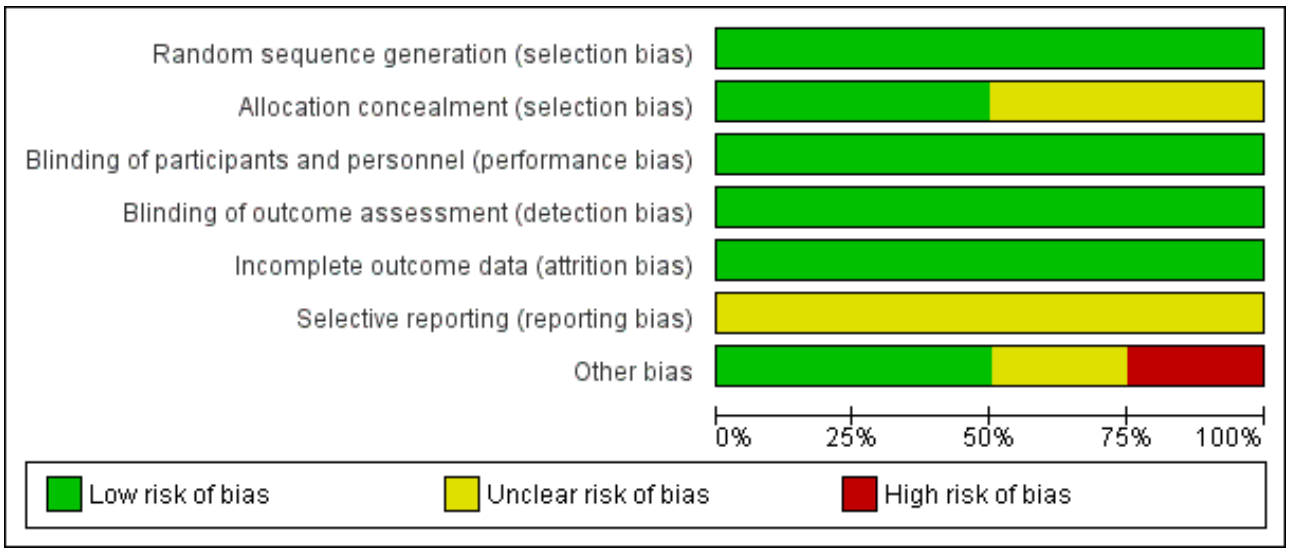
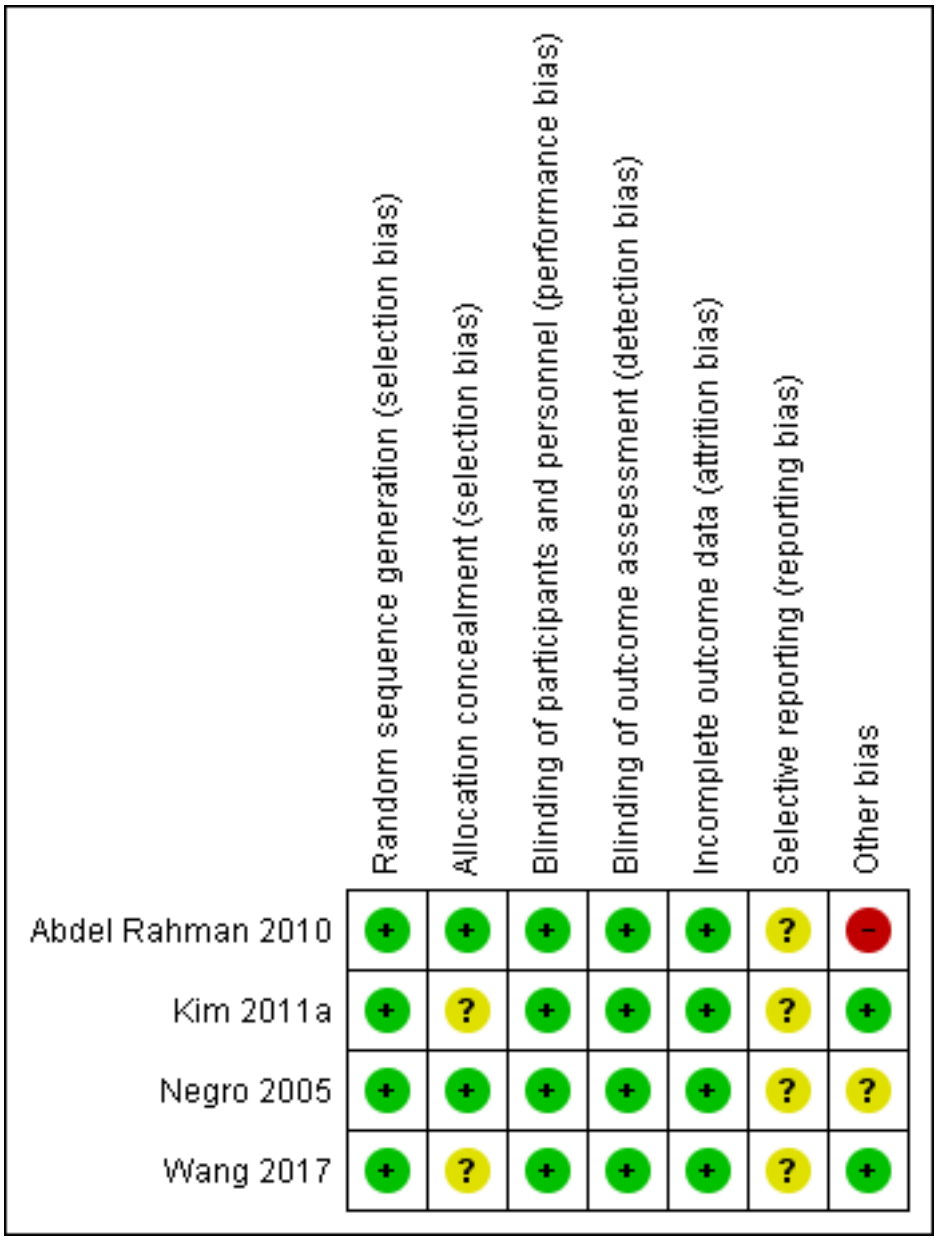


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation: all four studies were at low risk of bias for random sequence generation as they used a computer-generated random number sequence (Abdel Rahman 2010; Kim 2011a; Negro 2005; Wang 2017).

Allocation concealment: two of the studies were at low risk of bias as they used opaque envelopes (Abdel Rahman 2010; Negro 2005). Kim 2011a was at unclear risk of bias as they reported using sealed envelopes but there were no details as to whether these were opaque or details on numbering. Wang 2017 was at unclear risk of bias as they did not mention details of concealment.

Blinding

Performance bias: all four studies were at low risk for performance bias (Abdel Rahman 2010; Kim 2011a; Negro 2005; Wang 2017).

Detection bias: two studies did not report blinding, but were at low risk of performance and detection bias due to all outcomes being objective and unlikely to be influenced by blinding (Kim 2011a; Wang 2017). The remaining two studies were at low risk for detection bias (Abdel Rahman 2010; Negro 2005).

Incomplete outcome data

All four studies reported on all included participants and were at low risk of attrition bias (Abdel Rahman 2010; Kim 2011a; Negro 2005; Wang 2017).

Selective reporting

All four studies reported on important pregnancy outcomes, but did not report on adverse events or complications; hence, they were at unclear risk of reporting bias (Abdel Rahman 2010; Kim 2011a; Negro 2005; Wang 2017).

Other potential sources of bias

Abdel Rahman 2010 was at increased risk of bias due to incorrect reporting of statistical testing and results in the original publication. The correction published for this study remained implausible (100% clinical pregnancy rate in the experimental group with no failed implantation and no biochemical miscarriages) (Braverman 2011). We contacted the authors but received no reply.

Effects of interventions

See: **Summary of findings for the main comparison** Thyroxine compared to placebo or no treatment for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism

The meta-analysis of all the included studies was not possible due to significant interstudy variability in terms of inclusion criteria and interventions. Overall heterogeneity was significant (I^2 = 85%); therefore, we did not combine studies in a meta-analysis. Two studies were similar in terms of inclusion criteria and interventions and their results were pooled as their subgroup analysis was planned in the protocol (Negro 2005; Wang 2017). We report on the effects of interventions on individual basis for the remaining two studies (Abdel Rahman 2010; Kim 2011a).

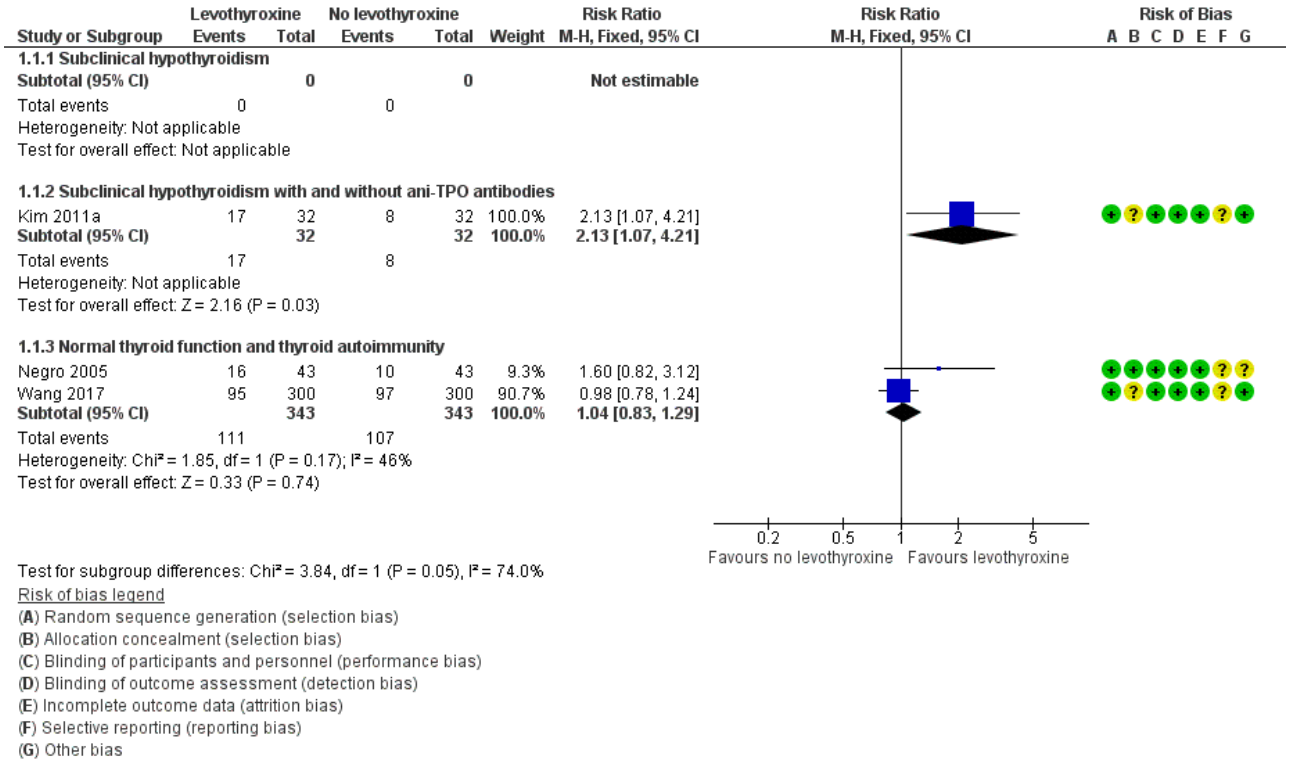
1 Thyroxine versus placebo or no treatment

Primary outcome

1.1 Live birth rate

See Analysis 1.1; Figure 4.

Figure 4. Forest plot of comparison: 1 Thyroxine versus placebo or no treatment, outcome: 1.1 Live birth rate per woman randomised.



All four studies reported on live birth.

1.1.1 Women with subclinical hypothyroidism

Two studies reported on women with subclinical hypothyroidism (Abdel Rahman 2010; Kim 2011a).

The data from Abdel Rahman 2010 were inconsistent between two publications and we were unable to get clarification so on advice from CGF editors we have not reported the data from this study.

Based on data reported byKim 2011a, the evidence suggested that thyroxine replacement may have improved live birth rates for women diagnosed with subclinical hypothyroidism and positive or negative anti-TPO antibodies (RR 2.13, 95% CI 1.07 to 4.21; 1 RCT, n = 64; low-quality evidence). This suggested that women with subclinical hypothyroidism and positive or negative anti-TPO antibodies would have a 25% chance of a live birth with placebo or no treatment, and 27% to 100% chance with thyroxine.

1.1.2 Women with normal thyroid function and thyroid autoimmunity

In women with normal thyroid function and thyroid autoimmunity, treatment with thyroxine replacement compared with placebo or no treatment may have led to similar live birth rates (RR 1.04, 95% CI 0.83 to 1.29; 2 RCTs, n = 686; low-quality evidence) (Negro 2005; Wang 2017). This suggested that women with normal thyroid function and thyroid autoimmunity would have a 31% chance of a live birth with placebo or no treatment and a 26% to 40% chance with thyroxine. Heterogeneity between the two studies including women with normal thyroid function and thyroid autoimmunity was moderate (I^2 = 46%). In a sensitivity analysis adopting the random-effects model, the results were similar (RR 1.13, 95% CI 0.73 to 1.75; 2 RCTs, n = 686; I^2 = 46%; low-quality evidence). There were similar results when the summary effect was calculated using odds ratio (OR 1.06, 95% CI 0.77 to 1.45; 2 RCTs, n = 686; I^2 = 47%; low-quality evidence).

1.2 Adverse events

Kim 2011a reported no preterm births in the experimental group and one preterm birth in the control group. Wang 2017 reported 21 preterm births in the experimental group and 19 preterm births in the control group.

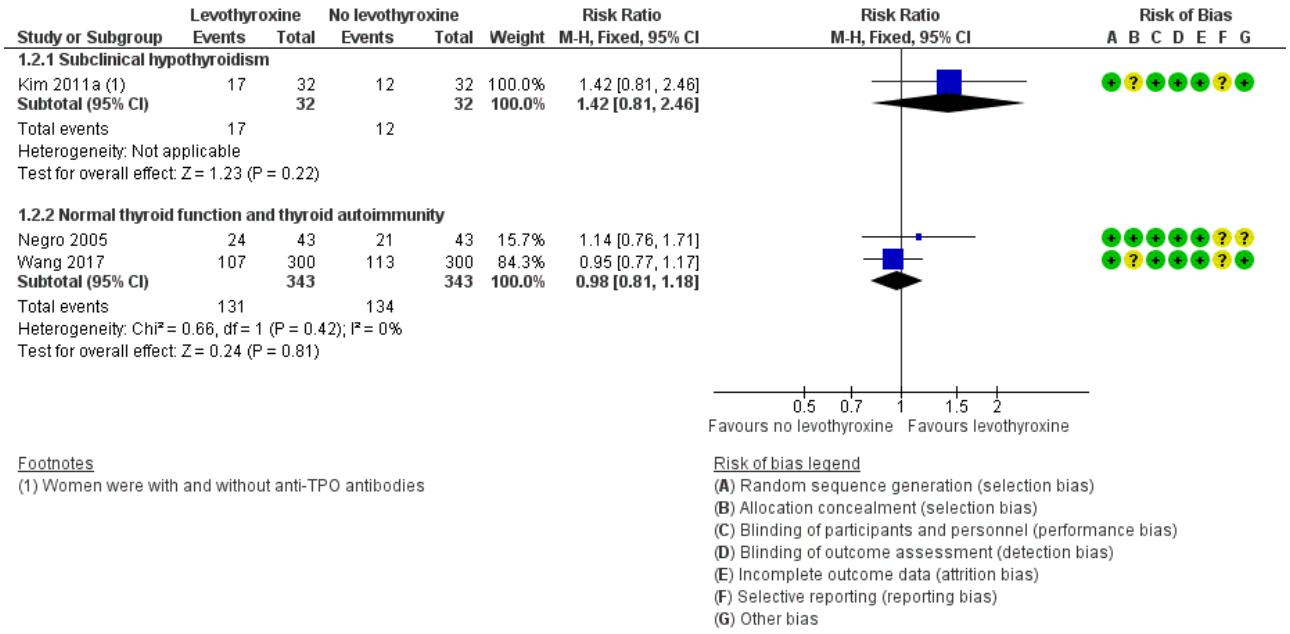
None of the RCTs reported on other direct adverse effects of thyroxine (allergic reactions, hyperthyroidism) or maternal pregnancy complications or foetal complications that could be linked to thyroxine treatment.

Secondary outcomes

1.3 Clinical pregnancy rate per woman randomised

See Analysis 1.2; Figure 5.

Figure 5. Forest plot of comparison: 1 Thyroxine versus placebo or no treatment, outcome: 1.2 Clinical pregnancy rate.



All four studies reported on clinical pregnancy.

1.3.1 Women with subclinical hypothyroidism

2 studies reported on women with subclinical hypothyroidism (Abdel Rahman 2010; Kim 2011a). On advice from CGF editors we have not reported the data from Abdel Rahman 2010.

Based on data reported by Kim 2011a, there may have been little or no difference in clinical pregnancy rates between the thyroxine replacement and no treatment groups for women diagnosed with subclinical hypothyroidism and positive or negative anti-TPO antibodies (RR 1.42, 95% CI 0.81 to 2.46; 1 RCT, n = 64).

1.3.2 Women with normal thyroid function and thyroid autoimmunity

There may have been little or no difference in clinical pregnancy rates between thyroxine and no treatment in women with normal thyroid function and thyroid autoimmunity (RR 0.98, 95% CI 0.81 to 1.18; 2 RCTs, n = 686) (Negro 2005; Wang 2017). Heterogeneity was low (Chi² = 0.66, df = 1, P = 0.42, I^2 = 0%).

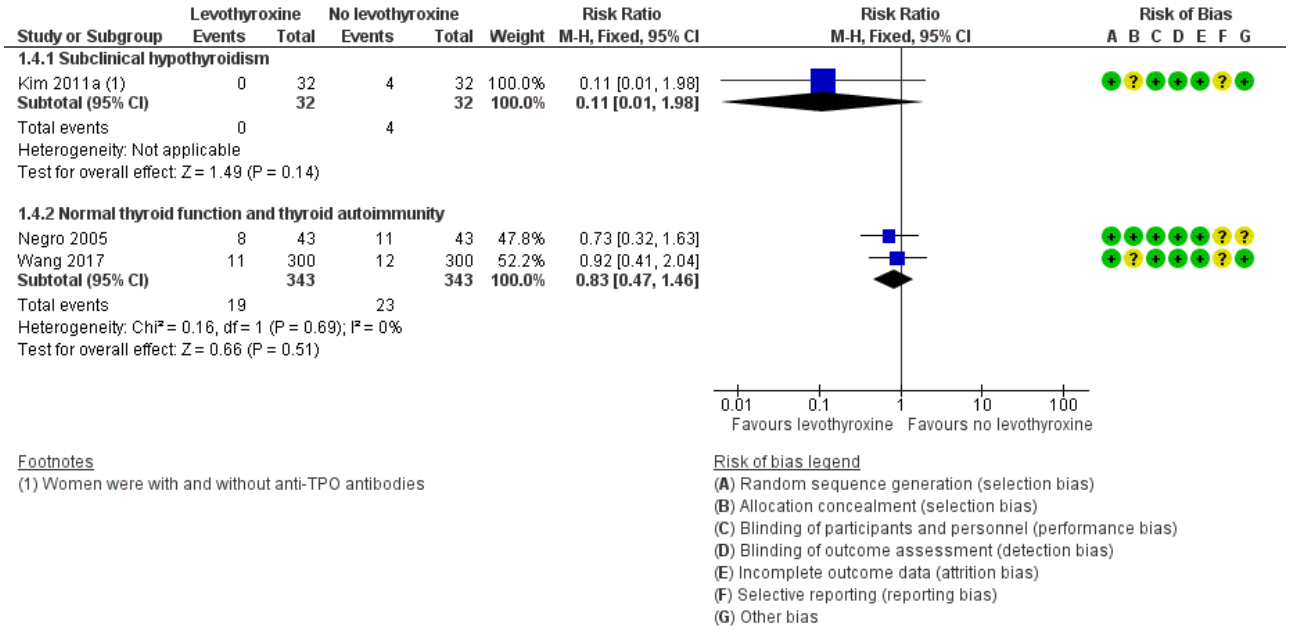
1.4 Multiple pregnancy rate per woman randomised

Based on data reported by Wang 2017, there may have been little or no difference in multiple pregnancy rates between the thyroxine replacement and no treatment groups (RR 1.22, 95% CI 0.79 to 1.89; 1 RCT, n = 600).

1.5 Miscarriage rate per woman randomised

See Analysis 1.4; Figure 6.

Figure 6. Forest plot of comparison: 1 Thyroxine versus placebo or no treatment, outcome: 1.4 Miscarriage rate per woman randomised.



All four studies reported on miscarriage.

1.5.1 Women with subclinical hypothyroidism

Two studies reported on women with subclinical hypothyroidism; we have not pooled their data.

On advice from CGF editors we have not reported the data from Abdel Rahman 2010.

Based on data reported by Kim 2011a, there may have been little or no difference in miscarriage rates between the thyroxine replacement and no treatment groups for women diagnosed with subclinical hypothyroidism and positive or negative anti-TPO antibodies (RR 0.11, 95% CI 0.01 to 1.98; 1 RCT, n = 64).

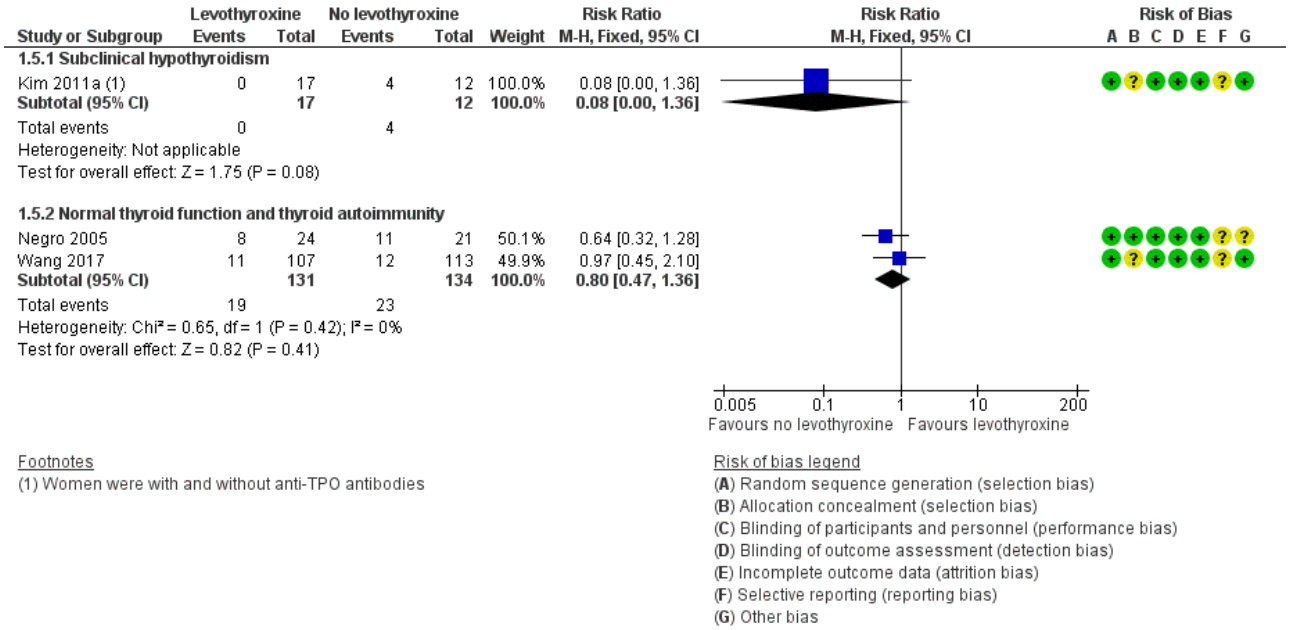
1.5.2 Women with normal thyroid function and thyroid autoimmunity

Treatment of women with normal thyroid function and thyroid autoimmunity with thyroxine replacement compared with placebo or no treatment may have led to similar miscarriage rates (RR 0.83, 95% CI 0.47 to 1.46; 2 RCTs, n = 686) (Negro 2005; Wang 2017). Heterogeneity was low ($Chi^2 = 0.16$, df = 1, P = 0.69, $I^2 = 0\%$).

1.6 Miscarriage per pregnancy

See Analysis 1.5; Figure 7.

Figure 7. Forest plot of comparison: 1 Thyroxine versus placebo or no treatment, outcome: 1.5 Miscarriage per clinical pregnancy.



1.6.1 Women with subclinical hypothyroidism

On advice from CGF editors we have not reported the data from Abdel Rahman 2010.

Based on data reported by Kim 2011a, there may have been little or no difference in miscarriage rates between the thyroxine replacement and no treatment groups for women diagnosed with subclinical hypothyroidism and positive or negative anti-TPO antibodies (RR 0.08, 95% CI 0.00 to 1.36; 1 RCT, n = 29).

1.6.2 Women with normal thyroid function and thyroid autoimmunity

Treatment of women with normal thyroid function and thyroid autoimmunity with thyroxine replacement compared with placebo or no treatment may have led to similar miscarriage rates (RR 0.80, 95% CI 0.47 to 1.36; 2 RCTs, n = 265) (Negro 2005; Wang 2017). Heterogeneity was low ($Chi^2 = 0.65$, df = 1, P = 0.42, $I^2 = 0\%$).

DISCUSSION

Summary of main results

Meta-analysis of all the included studies was not possible due to significant interstudy variability in terms of inclusion criteria and interventions. Overall heterogeneity was significant and we planned not to combine studies in a meta-analysis if heterogeneity was significant. Women with subclinical hypothyroidism and women with normal thyroid function and thyroid autoimmunity were considered different populations.

Abdel Rahman 2010 included 70 women with subclinical hypothyroidism with no testing for autoimmune antibody; the dose of thyroxine was individually adjusted to achieve TSH level less than 4.0 mIU/L prior to ART. This meant that there was a more pronounced effect of thyroxine replacement as women had much higher normal values of TSH before starting the ART than other studies. We were uncertain of the reported results and have not included their data in our analyses.

Kim 2011a included 64 women with subclinical hypothyroidism and thyroid antibodies were also tested. In the no treatment group, thyroid antibodies were higher in the subgroup with miscarriage compared to the subgroup with delivery; however, thyroid antibody levels were similar in the treated group. In the treatment group, thyroxine replacement were given in a dose of 50 µg and titrated thereafter to achieve TSH level less than 2.5 mIU/L. Women developing hypothyroidism during pregnancy in the control group were also given thyroxine replacement, which might have skewed results. This study also did not present subgroup outcome data for women who were thyroid antibody positive or negative with subclinical hypothyroidism in treatment and control groups. Thyroxine replacement was associated with an increase in live birth rate although there was no clear evidence of a difference between groups for clinical pregnancy rate. This study reported miscarriage per clinical pregnancy, not per woman randomised, when miscarriage rate per woman randomised was examined, there was no clear evidence of a difference.

Negro 2005 and Wang 2017 included 686 women with normal thyroid function and thyroid autoimmunity and found that levothyroxine and no treatment may have led to similar results in terms of live birth, clinical pregnancy rate, miscarriage rate and multiple or preterm birth rates. Wang 2017 titrated the dose of levothyroxine (25 µg or 50 µg) aiming for a TSH level within 0.1 mIU/L to 2.5 mIU/L in the first trimester, 0.2 mIU/L to 3.0 mIU/L in the second trimester and 0.3 mIU/L to 3.0 mIU/L in the third trimester. Negro 2005 offered a constant dose of 1 mg/kg/day irrespective of the TSH level.

None of the studies reported on maternal pregnancy complications, foetal complications or adverse effects of thyroxine.

Overall completeness and applicability of evidence

The current evidence was limited by volume as only four studies were identified. The populations and regimens for the experimental interventions differed. As all the including populations in all four studies were so different, it was inappropriate to pool them all for statistical analysis.

Women having subclinical hypothyroidism could have unknown autoimmune antibodies status (Abdel Rahman 2010), or either presence or absence of autoimmune thyroid antibodies (Kim 2011a).

Two RCTs included women with normal thyroid function and thyroid autoimmunity (Negro 2005; Wang 2017).

We do not believe that the evidence was generalisable to all settings. More high-quality evidence is required using levothyroxine in subfertile women with subclinical hypothyroidism or normal thyroid function and thyroid autoimmunity.

Quality of the evidence

Overall the included studies were at low risk of bias according to the criteria specified by the *Cochrane Handbook for Systematic Reviews of Interventions*. Using GRADE methodology, the quality of evidence for the primary outcome of live birth was very low to low.

Potential biases in the review process

We tried to minimise potential biases in the review process by conducting a systematic search of multiple databases. Two review authors independently selected studies for inclusion and extracted data.

Agreements and disagreements with other studies or reviews

A systematic review published in 2013 included three of the studies that we have identified in this review (Velkeniers 2013). However, they pooled their data in a meta-analysis despite reporting an I^2 statistic of 70% for live birth and 82% for clinical pregnancy. They could not explain the observed heterogeneity. They reported that thyroxine replacement was associated with a higher live birth rate, no clear evidence of a difference in clinical pregnancy rate and a decreased miscarriage rate. We did not pool the data in a meta-analysis and, therefore, we could not directly compare findings.

A more recent systematic review published in 2018 pooled the data of all four studies included in the present review despite reporting an I^2 statistic of 84%. They reported a reduction in the risk of miscarriage, but no improvement in the rates of clinical pregnancy, live birth and preterm birth (Rao 2018).

The TABLET trial included 952 women diagnosed with anti-TPO antibodies following a history of recurrent miscarriage or infertility (Dhillon-Smith 2019). Trial authors concluded that levothyroxine treatment in euthyroid women with anti-TPO antibodies did not result in a higher rate of live births than placebo. Data from this trial could not be included in the present systematic review due to the heterogeneous population (women having spontaneous conceptions following recurrent miscarriage, or requiring IVF or other fertility treatments).

The National Institute of Health and Care Excellence (NICE), UK does not recommend routine testing of thyroid function tests unless women have symptoms of thyroid disease (NICE 2017).

However, the British Thyroid Association, UK suggests that women seeking fertility treatment should have thyroid tests as part of the workup for infertility. If hypothyroidism (overt or subclinical) is detected, this should be treated aiming for a TSH of less than 2.5 mIU/L or TSH within the first trimester-specific reference range if such ranges are available locally (British Thyroid Association).

The American Thyroid Association also recommends evaluation of serum TSH concentration for all women seeking infertility treatment (American Thyroid Association 2017). It recommends that women with subclinical hypothyroidism undergoing ART should be treated with thyroxine replacement with a treatment goal to achieve a TSH concentration less than 2.5 mIU/L. It also suggests that insufficient evidence exists for offering thyroxine replacement to improve fertility outcomes in women undergoing ART with euthyroid ATD but may be considered based on its potential benefits in comparison to its minimal risk.

European Thyroid Association guidelines recommend that subclinical hypothyroidism arising prior to conception or during gestation should be treated with thyroxine replacement as there is an increase in pregnancy loss, gestational diabetes, gestational hypertension, pre-eclampsia and preterm delivery in women with subclinical hypothyroidism in pregnancy (Lazarus 2014). The reference range upper limits of TSH in first trimester of pregnancy is 2.5 mIU/L. It also recommends that presence of thyroid antibodies prepregnancy is associated with hypothyroidism in pregnancy so thyroid function tests needs to repeat every four to six weeks.

The American Society for Reproductive Medicine Practice Committee recommends that there is enough evidence that subclinical hypothyroidism defined as a TSH level greater than 4 mIU/L during pregnancy is associated with miscarriage, but insufficient evidence that TSH levels between 2.5 mIU/L and 4 mIU/L are associated with miscarriage (ASRM Practice Committee 2015). It also recommends that thyroxine replacement in women with subclinical hypothyroidism (TSH greater than 4.0 mIU/L) is associated with improvement in pregnancy and miscarriage rates. There is insufficient evidence that thyroxine replacement in women with TSH levels between 2.5 mIU/L and 4 mIU/L is associated with improvement in pregnancy and miscarriage rates. It also suggests that there is enough evidence that thyroid antibodies are associated with miscarriage. Thyroxine replacement may improve pregnancy outcomes in women with positive thyroid antibodies, especially if the TSH level are greater than 2.5 mIU/L.

It is evident that there is no consensus target TSH to achieve prepregnancy in women without thyroid dysfunction. It is advised that women with thyroid dysfunction should aim for TSH of less than 4.0 mIU/L or 2.5 mIU/L prior to achieving pregnancy.

AUTHORS' CONCLUSIONS

Implications for practice

No clear conclusions can be drawn in this systematic review due to the very low to low quality of the evidence reported.

Implications for research

This systematic review identified the need for randomised controlled trials (RCT) looking at very specific populations either women with subclinical hypothyroidism with or without autoimmune thyroid antibodies or normal thyroid function and thyroid autoimmunity.

We suggest that future pragmatic RCTs may wish to look at one of these three populations:

- euthyroid women with ATD (TSH less than 4.0 mIU/L or 2.5 mIU/L);
- women with subclinical hypothyroidism without ATD (TSH greater than 4.0 mIU/L or 2.5 mIU/L);
- women with subclinical hypothyroidism with ATD (TSH greater than 4.0 mIU/L or 2.5 mIU/L).

Future RCTs should report on live birth and adverse events (including direct adverse effects of thyroxine, maternal pregnancy complications, foetal complications) as primary outcomes to allow the quantification of the overall effect and the safety profile of the intervention.

ACKNOWLEDGEMENTS

We thank Dr Gordana Prelevic for her expert advice on autoimmune thyroid disease. We thank Dr David Owen and Dr Panagiotis Peitsidis for their contributions to the protocol.

We thank Helen Nagels (Managing Editor), Marian Showell (Information Specialist) and the editorial board of the Cochrane Gynaecology and Fertility Group for their invaluable assistance in developing the protocol and review.

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CHARACTERISTICS OF STUDIES

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

Abdel Rahman 2010

Methods	Design: 2-armed parallel RCT
Participants	Number: 70 Age (mean years; experimental vs control): 31.2 vs 30 Inclusion criteria: aged 20–40 years; regular menstrual cycles (21–35 days); and normal thyroid ultrasonography findings with thyroid volume of 18 mL and no morphological lesions, mild thyroid failure (subclinical hypothyroidism). Exclusion criteria: history of thyroid disease, goitre (thyroid volume > 18 mL), or other morphological thyroid anomalies, including nodules or increased basal prolactin concentration > 25 ng/mL. Ovarian controlled hyperstimulation: long agonist protocol Fertilisation: ICSI Stage of the embryo at transfer: not mentioned Embryo processing: not mentioned (likely fresh) Number of embryos transferred: 1–3 Location: Shatby University Hospital for Women in Alexandria, Egypt Period: April 2006 to April 2007
Interventions	Experimental: 1 month before the ART, women underwent levothyroxine replacement with an oral dose of 50–100 µg every morning. The levothyroxine dosage was empirical and began with a small dose of 50 µg and was then gradually adjusted to normalise TSH before IVF. The same treatment was continued during pregnancy. Control: placebo
Outcomes	Clinical pregnancy, miscarriage, live birth
Notes	Power calculation: no Funding: not mentioned

Abdel Rahman 2010 *(Continued)*

	Trial registration: not mentioned Publication type: full text. Correction data for Rahman 2010 were published in Braverman 2011. Rahman 2010 reported percentages that did not lead to rounded population numbers. The correction published by Braverman 2011 reports absolute numbers inconsistent with those in the original paper. We attempted to contact the authors several times (last time in March 2019) for clarifications, but we have received no reply; hence, on advice from CGF we have not included this study in our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer program (SPSS version 10; SPSS, Inc, Chicago, IL) used to randomly assign the infertile women with subclinical hypothyroidism to 1 of 2 groups.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelope assigned to each woman.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only the physician applying the treatment knew which group each woman had been assigned to; the physician did not participate in any subsequent phase of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only the physician applying the treatment knew which group each woman had been assigned to; the physician did not participate in any subsequent phase of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant was lost to follow-up or abandoned the study.
Selective reporting (reporting bias)	Unclear risk	Reported on important outcomes, but not on complications/adverse effects.
Other bias	High risk	Incorrect statistical tests in original publication and implausible results published in correction (100% clinical pregnancy rate; 13 miscarriages out of 10 clinical pregnancies).

Kim 2011a

Methods	Design: 2-armed parallel RCT
Participants	Number: 64 Age (mean years; experimental vs control): 36.0 vs 36.1 Inclusion criteria: infertile women with subclinical hypothyroidism who had undergone IVF/ICSI Exclusion criteria: not mentioned Ovarian controlled hyperstimulation: GnRH antagonist multiple-dose protocol Fertilisation: IVF/ICSI Stage of the embryo at transfer: cleavage Embryo processing: fresh

Kim 2011a *(Continued)*

	Number of embryos transferred: 1–4 Location: Asan Medical Center, Seoul, South Korea Period: March 2006 to September 2009
Interventions	Experimental: levothyroxine 50 µg (Synthyroxine; Dalim BioTec, Seoul, South Korea) administered every morning from the first day of COS and continued up to the day of serum beta-hCG measurement. Serum TSH and FT4 were also measured at the same time as serum beta-hCG was measured. If pregnancy was confirmed, an adequate dose of levothyroxine was given continuously throughout the pregnancy. Control: even in pregnant women included in the control group, an adequate dose of levothyroxine was supplemented when overt hypothyroidism was detected during pregnancy.
Outcomes	Clinical pregnancy, miscarriage, live birth
Notes	26 women in experimental group and 25 women in control group had anti-TPO antibodies Power calculation: no Funding: not mentioned Trial registration: not mentioned Publication type: full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list.
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes. No information provided if they were opaque or numbered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not mentioned, but unlikely to affect outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned, but unlikely to affect outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant was lost to follow-up or abandoned the study.
Selective reporting (reporting bias)	Unclear risk	Reported on important outcomes, but not on complications/adverse effects.
Other bias	Low risk	No evidence of other bias.

Negro 2005

Methods	Design: 2-armed parallel RCT

Negro 2005 *(Continued)*

Participants	Number: 72 Age (mean years; experimental vs control): 29.2 vs 30.1 Inclusion criteria: infertile women, anti-TPO positive, undergoing ART. Exclusion criteria: women with overt thyroid dysfunction. Ovarian controlled hyperstimulation: recombinant FSH (Puregon; NV Organon, The Netherlands) and GnRH antagonist (Orgalutran; NV Organon). Fertilisation: conventional IVF or ICSI Stage of the embryo at transfer: not mentioned Embryo processing: not mentioned (likely fresh) Number of embryos transferred: 1–3 Location: Department of Endocrinology, District Hospital 'Vito Fazzi', Italy Period: January 1999 to January 2003
Interventions	Experimental: 1 month before ART, women underwent levothyroxine replacement 1 mg/kg/day and continued it throughout pregnancy. (Note: likely dose was 1 µg/kg/day.) Control: placebo.
Outcomes	Clinical pregnancy, miscarriage, live birth
Notes	Power calculation: no Funding: not mentioned Trial registration: not mentioned Publication type: full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer program to randomly assign the participants to 1 or the other group.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelope assigned to each participant and only the doctor applying the treatment knew which group each participant had been assigned to, and did not participate in any subsequent phase of the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medical doctors attended different phases of the protocol so that each was blinded to which group the participants belonged.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medical doctors attended different phases of the protocol so that each was blinded to which group the participants belonged.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant was lost to follow-up or abandoned the study.

Negro 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Reported on important outcomes, but not on complications/adverse effects.
Other bias	Unclear risk	Discrepancy between results reported in text vs tables.

Wang 2017

Methods	Design: 2-armed parallel RCT
Participants	Number: 600 Age (mean years; experimental vs control): 31.3 vs 31.7 Inclusion criteria: women undergoing ART, aged 23–40 years, body mass index < 35. Exclusion criteria: women taking a thyroid hormone or antithyroid medication or who had undergone thyroid surgery or radioiodine treatment were excluded from the trial. Women were not eligible if they had ≥ 2 spontaneous miscarriages; known diabetes mellitus or other endocrinological or metabolic diseases; tested positive for the anticardiolipin antibody, antinuclear antibody or lupus anticoagulants; serum alanine aminotransferase and aspartate aminotransferase levels > 2 times the upper limit of normal; serum creatinine concentration > 1.47 mg/dL (130 µmol/L); or were taking adjuvant treatments, such as anticoagulants, glucocorticoids or other relevant treatments. Ovarian controlled hyperstimulation: eligible participants underwent IVF embryo transfer according to 1 of 4 conventional protocols. Fertilisation: IVF or ICSI Stage of the embryo at transfer: day 3 Embryo processing: fresh Number of embryos transferred: 1–3 Location: Peking University Third Hospital, Beijing, China Period: 6 September 2012 to 15 June 2016
Interventions	Experimental: levothyroxine replacement started 2–4 weeks before the controlled ovarian hyperstimulation and continued through the end of pregnancy. For women with TSH level ≥ 2.5 mIU/L, starting dose was 50 µg/day; for women with TSH level < 2.5 mIU/L, starting dose was 25 µg/day. For women with bodyweight < 50 kg, the starting dose was decreased by 50%. The levothyroxine dose was titrated to keep the TSH level within 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester and 0.3–3.0 mIU/L in the third trimester. Control: no levothyroxine, but otherwise same care.
Outcomes	Miscarriage, clinical pregnancy, multiple pregnancy, preterm deliveries
Notes	Power calculation: yes Funding: grants 2015BAI13B06 from the National Key Technology R&D Program and 2012CB517502 and from the Chinese National 973 Program, both from the Ministry of Science and Technology of China. Trial registration: Chinese Clinical Trial Registry: ChiCTR-TRC-13004097 Publication type: full text
Risk of bias	

Wang 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence generated in a 1:1 ratio by producing a 600 unique random-number list using EpiCalc 2000 software (www.brixton-health.com/epicalc.html), in which the even number was assigned to the intervention and the odd number to the control.
Allocation concealment (selection bias)	Unclear risk	No details mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded, but unlikely to affect outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to affect outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for.
Selective reporting (reporting bias)	Unclear risk	Reported on important outcomes, but not on complications/adverse effects.
Other bias	Low risk	No evidence of other bias.

ART: assisted reproduction treatment; COS: controlled ovarian stimulation; FT4: free thyroxine; FSH: follicle-stimulating hormone; GnRH: gonadotrophin-releasing hormone; hCG: human chorionic gonadotrophin; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilisation; RCT: randomised controlled trial; TSH: thyroid-stimulating hormone.

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

Study	Reason for exclusion
Blumenthal 2017	Study not related to ART.
Busnelli 2016	Systematic review
De Brucker 2016	Not randomised
Dhillon-Smith 2019	Heterogeneous population of IVF and other fertility treatments or spontaneous conceptions after recurrent miscarriage
Maraka 2016	Study not related to ART
Mintziori 2016	Review
Mumuşoğlu 2016	Cohort study
Nazarpour 2017	Study not related to ART
Negro 2006	Study not related to ART

Study	Reason for exclusion
Rao 2018	Systematic review
Riestenberg 2016	Retrospective
Velkeniers 2013	Systematic review

ART: assisted reproduction treatment.

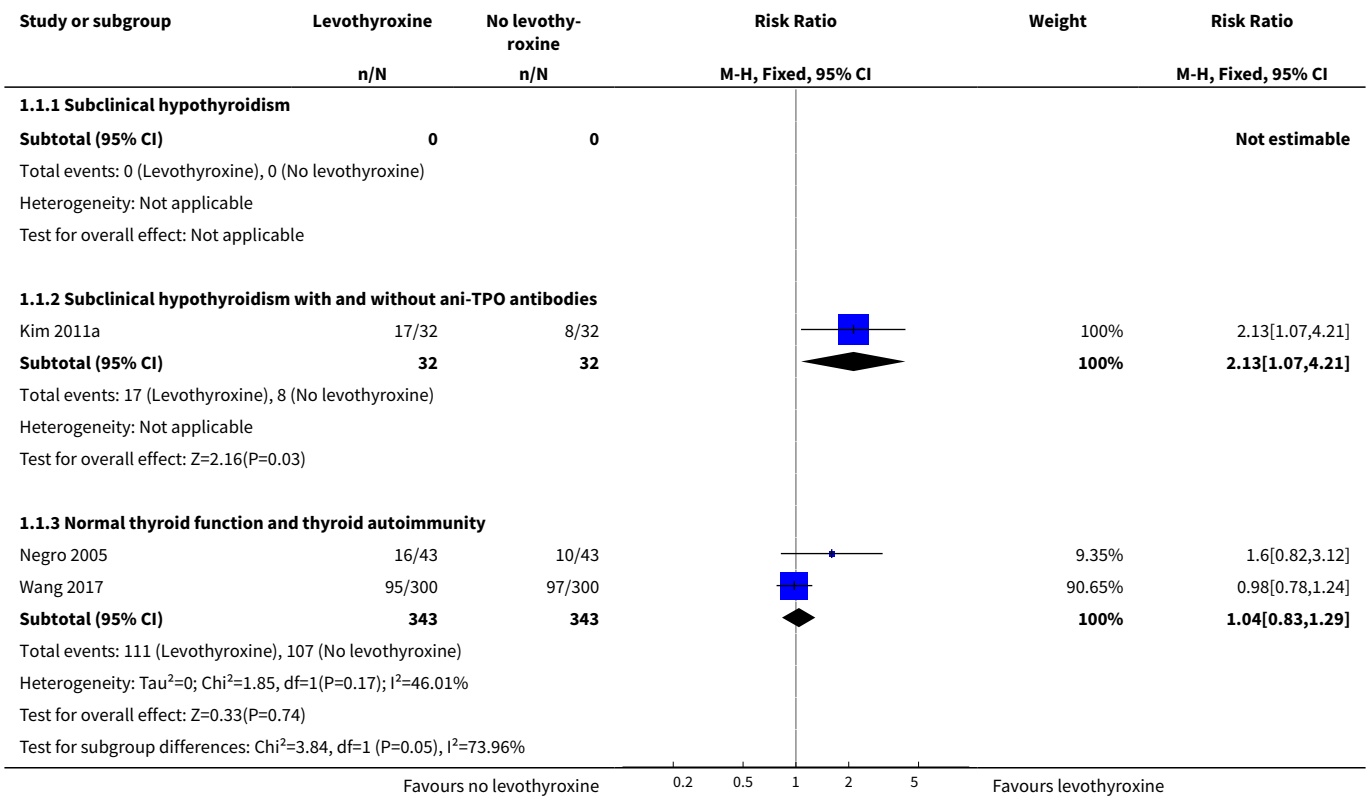
DATA AND ANALYSES

Comparison 1. Thyroxine versus placebo or no treatment

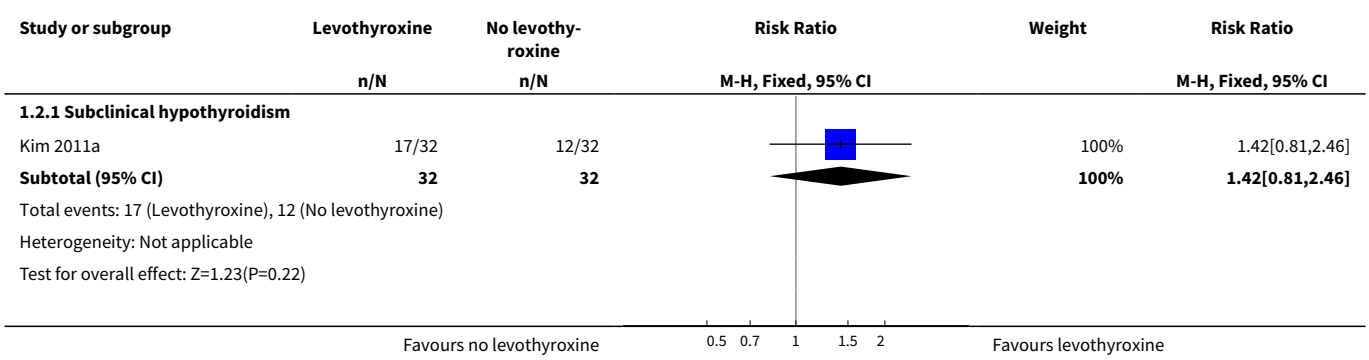
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman randomised	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Subclinical hypothyroidism	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Subclinical hypothyroidism with and without ani-TPO antibodies	1	64	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [1.07, 4.21]
1.3 Normal thyroid function and thyroid autoimmunity	2	686	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.83, 1.29]
2 Clinical pregnancy rate	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Subclinical hypothyroidism	1	64	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.81, 2.46]
2.2 Normal thyroid function and thyroid autoimmunity	2	686	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.18]
3 Multiple pregnancy rate	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Normal thyroid function and thyroid autoimmunity	1	600	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.79, 1.89]
4 Miscarriage rate per woman randomised	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Subclinical hypothyroidism	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.98]
4.2 Normal thyroid function and thyroid autoimmunity	2	686	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.47, 1.46]
5 Miscarriage per clinical pregnancy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

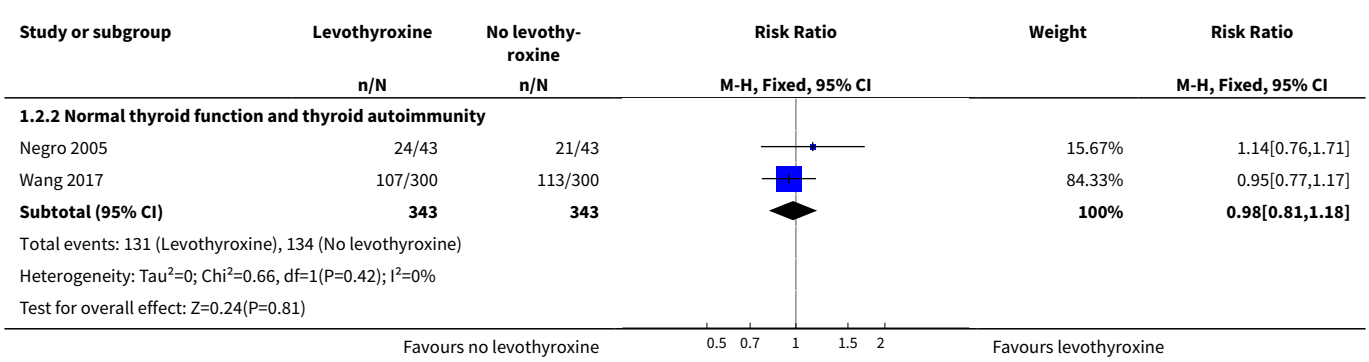
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Subclinical hypothyroidism	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.36]
5.2 Normal thyroid function and thyroid autoimmunity	2	265	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.47, 1.36]

Analysis 1.1. Comparison 1 Thyroxine versus placebo or no treatment, Outcome 1 Live birth rate per woman randomised.

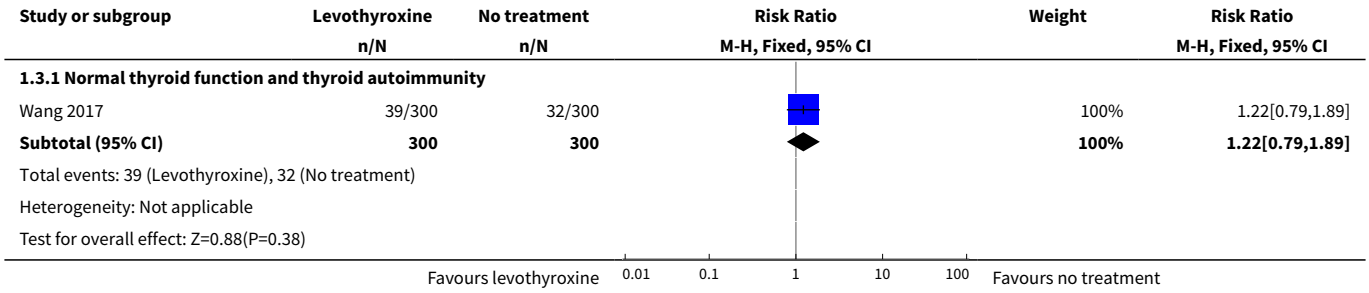


Analysis 1.2. Comparison 1 Thyroxine versus placebo or no treatment, Outcome 2 Clinical pregnancy rate.

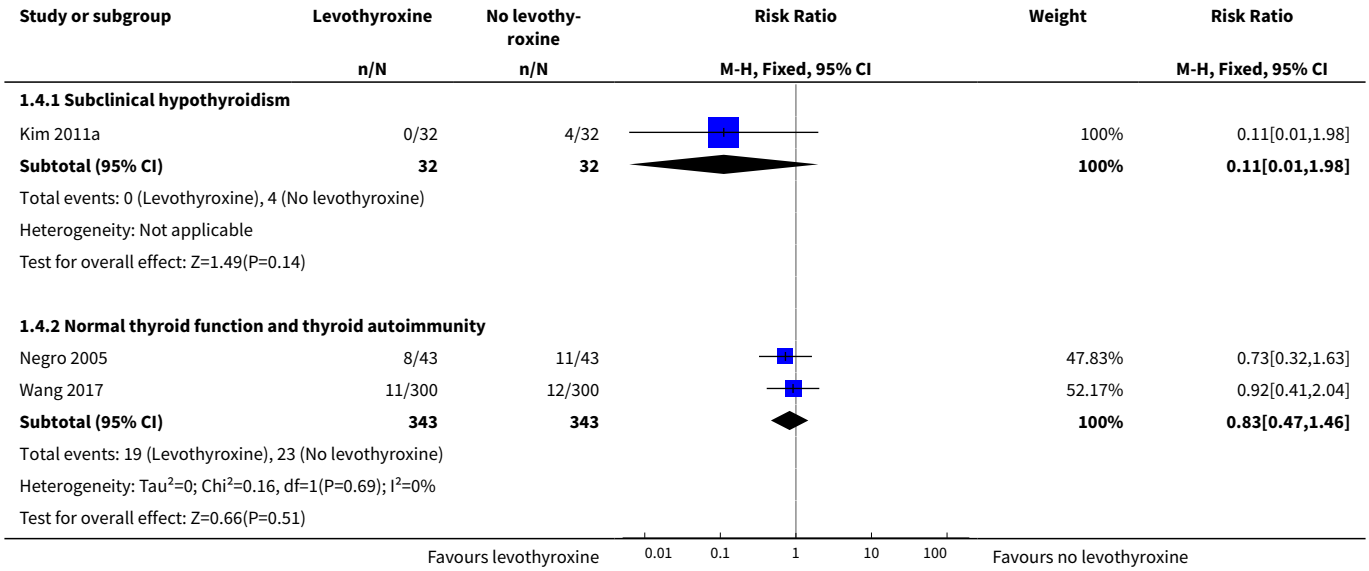




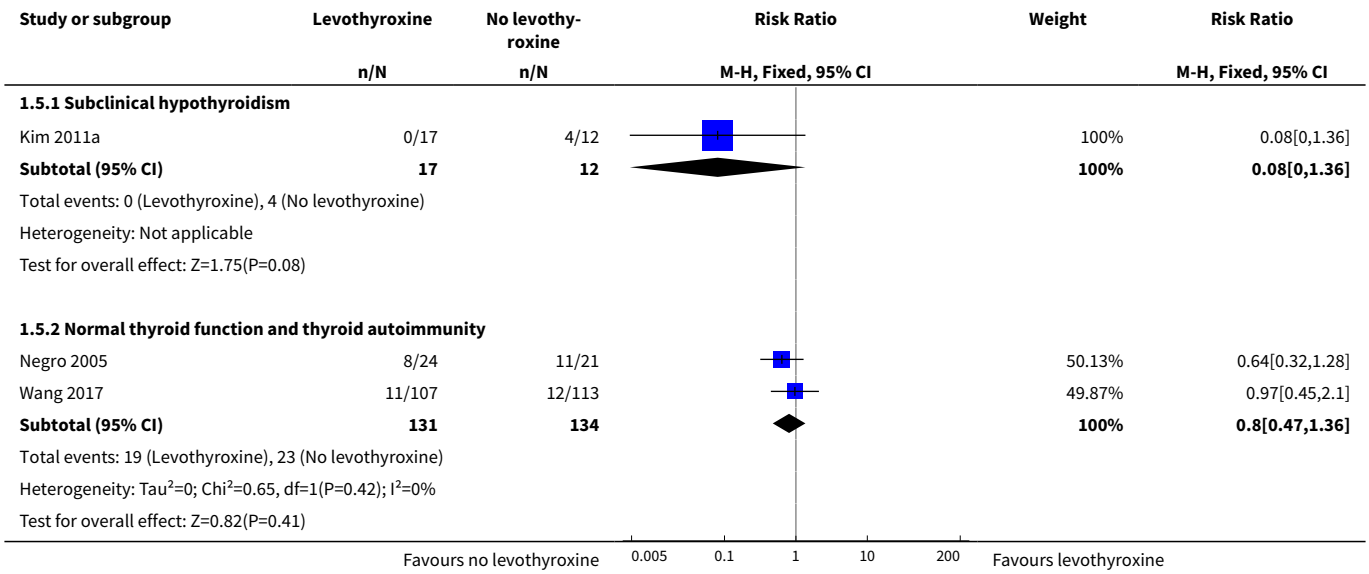
Analysis 1.3. Comparison 1 Thyroxine versus placebo or no treatment, Outcome 3 Multiple pregnancy rate.



Analysis 1.4. Comparison 1 Thyroxine versus placebo or no treatment, Outcome 4 Miscarriage rate per woman randomised.



Analysis 1.5. Comparison 1 Thyroxine versus placebo or no treatment, Outcome 5 Miscarriage per clinical pregnancy.



APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility specialised register search strategy

PROCITE platform

Searched 8 April 2019

Keywords CONTAINS "IVF" or "in vitro fertilisation" or "in vitro fertilization" or "in vitro maturation" or "in vivo maturation" or "ICSI" or "intracytoplasmic sperm injection" or "Intrauterine Insemination" or "ART" or "artificial insemination" or "IUI" or "*Embryo Transfer" or "blastocyst transfer" or "assisted reproduction techniques" or "assisted reproduction" or "assisted conception" or "subfertility" or "subfertility-Female" or "infertile" or "infertility" or Title CONTAINS "IVF" or "in vitro fertilisation" or "in vitro fertilization" or "in vitro maturation" or "in vivo maturation" or "ICSI" or "intracytoplasmic sperm injection" or "Intrauterine Insemination" or "ART" or "artificial insemination" or "IUI" or "*Embryo Transfer" or "blastocyst transfer" or "assisted reproduction techniques" or "assisted reproduction" or "assisted conception" or "subfertility" or "subfertility-Female" or "infertile" or "infertility"

AND

Keywords CONTAINS "thyroid" or "thyroid dysfunction" or "thyroid function" or "thyroid function temperature" or "Thyroxine levels" or "levothyroxine" or "hypothyroid" or Title CONTAINS "thyroid" or "thyroid dysfunction" or "thyroid function" or "thyroid function temperature" or "Thyroxine levels" or" levothyroxine" or "hypothyroid" (46 hits)

Appendix 2. CENTRAL search strategy

CRSO Web platform

Searched 8 April 2019

#1 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES 1047
#2 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES 1977
#3 MESH DESCRIPTOR Sperm Injections, Intracytoplasmic EXPLODE ALL TREES 515
#4 (embryo* adj2 transfer*):TI,AB,KY 3725
#5 (vitro fertili?ation):TI,AB,KY 3190
#6 ivf:TI,AB,KY 5272
#7 icsi:TI,AB,KY 2560
#8 (intracytoplasmic sperm injection*):TI,AB,KY 1815

#9 (blastocyst* adj2 transfer*):TI,AB,KY 392
#10 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES 3031
#11 (assisted reproduct*):TI,AB,KY 1348
#12 (artificial insemination):TI,AB,KY 232
#13 MESH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES 358
#14 IUI:TI,AB,KY 832
#15 (intrauterine insemination*):TI,AB,KY 943
#16 (ovulation induc*):TI,AB,KY 2454
#17 (ovar* adj2 stimulat*):TI,AB,KY 2116
#18 superovulat*:TI,AB,KY 212
#19 (ovarian hyperstimulation):TI,AB,KY 1386
#20 COH:TI,AB,KY 377
#21 infertil*:TI,AB,KY 7787
#22 subfertil*:TI,AB,KY 888
#23 (ovar* adj2 induction):TI,AB,KY 227
#24 superovulat*:TI,AB,KY 212
#25 (euthyroid adj5 wom?n):TI,AB,KY 55
#26 (hypothyroid* adj5 wom?n):TI,AB,KY 61
#27 (recurrent miscarriage*):TI,AB,KY 240
#28 (pregnancy adj3 loss*):TI,AB,KY 601
#29 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 or #28 14432
#30 MESH DESCRIPTOR Thyroxine EXPLODE ALL TREES 1022
#31 Thyroxine:TI,AB,KY 1823
#32 triiodothyronine:TI,AB,KY 926
#33 Levothyroxine:TI,AB,KY 665
#34 L-thyroxine:TI,AB,KY 196
#35 liotrix:TI,AB,KY 5
#36 liothyronine:TI,AB,KY 382
#37 Levothroid:TI,AB,KY 4
#38 (Levoxyl or Synthroid or Unithroid):TI,AB,KY 18
#39 Tetraiodothyronine:TI,AB,KY 11
#40 eltroxin:TI,AB,KY 5
#41 (l-thyroxin or levothyroxin):TI,AB,KY 51
#42 (thyroxin or eltroxine):TI,AB,KY 138
#43 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 2487
#44 #29 AND #43 111

Appendix 3. MEDLINE search strategy

Ovid platform

Searched from 1946 to 8 April 2019

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (39613)
2 embryo transfer$.tw. (11078)
3 vitro fertili?ation.tw. (21650)
4 ivf-et.tw. (2209)
5 ivf.tw. (22020)
6 icsi.tw. (7738)
7 intracytoplasmic sperm injection$.tw. (6693)
8 (blastocyst adj2 transfer$).tw. (926)
9 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (65928)
10 assisted reproduct$.tw. (13572)
11 artificial insemination.tw. (6214)
12 iui.tw. (1635)
13 intrauterine insemination$.tw. (2353)
14 ovulation induc$.tw. (3999)
15 (ovari$ adj2 stimulat$).tw. (6580)
16 superovulat$.tw. (3304)
17 super-ovulat$.tw. (85)
18 ovarian hyperstimulation.tw. (4809)

19 COH.tw. (1620)
20 infertil$.tw. (56296)
21 subfertil$.tw. (4755)
22 (ovari$ adj2 induction).tw. (280)
23 (euthyroid adj5 women).tw. (535)
24 (hypothyroid$ and women).tw. (3116)
25 or/1-24 (132283)
26 exp Thyroxine/ (47530)
27 Thyroxine.tw. (26366)
28 triiodothyronine.tw. (16400)
29 Levothyroxine.tw. (3276)
30 L-thyroxine.tw. (2944)
31 liotrix.tw. (4)
32 liothyronine.tw. (238)
33 Levothroid.tw. (14)
34 (Levoxyl or Synthroid or Unithroid).tw. (66)
35 Tetraiodothyronine.tw. (282)
36 eltroxin.tw. (28)
37 l-thyroxin.tw. (280)
38 levothyroxin.tw. (74)
39 thyroxin.tw. (3163)
40 eltroxine.tw. (8)
41 or/26-40 (60331)
42 25 and 41 (1772)
43 randomized controlled trial.pt. (479393)
44 controlled clinical trial.pt. (93006)
45 randomized.ab. (438696)
46 randomised.ab. (87499)
47 placebo.tw. (201847)
48 clinical trials as topic.sh. (186556)
49 randomly.ab. (308363)
50 trial.ti. (196326)
51 (crossover or cross-over or cross over).tw. (79736)
52 or/43-51 (1267107)
53 exp animals/ not humans.sh. (4566442)
54 52 not 53 (1165487)
55 42 and 54 (170)

Appendix 4. Embase search strategy

Ovid platform

Searched from 1980 to 8 April 2019

1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (58432)
2 embryo$ transfer$.tw. (17939)
3 in vitro fertili?ation.tw. (26319)
4 icsi.tw. (13790)
5 intracytoplasmic sperm injection$.tw. (8257)
6 (blastocyst adj2 transfer$).tw. (1909)
7 ivf.tw. (34596)
8 exp infertility therapy/ or exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (85798)
9 assisted reproduct$.tw. (18830)
10 artificial insemination.tw. (5573)
11 iui.tw. (2788)
12 intrauterine insemination$.tw. (3280)
13 ovulation induc$.tw. (5180)
14 (ovari$ adj2 stimulat$).tw. (9546)
15 superovulat$.tw. (3527)
16 ovarian hyperstimulation.tw. (6694)
17 COH.tw. (2104)
18 infertil$.tw. (72517)

19 subfertil$.tw. (5975)
20 (ovari$ adj2 induction).tw. (329)
21 (euthyroid adj3 women).tw. (590)
22 (hypothyroid$ adj3 women).tw. (919)
23 or/1-22 (167501)
24 exp thyroxine/ (46353)
25 Thyroxine.tw. (25891)
26 triiodothyronine.tw. (15190)
27 Levothyroxine.tw. (4929)
28 L-thyroxine.tw. (3129)
29 liotrix.tw. (5)
30 liothyronine.tw. (263)
31 Levothroid.tw. (110)
32 (Levoxyl or Synthroid or Unithroid).tw. (712)
33 Tetraiodothyronine.tw. (304)
34 eltroxin.tw. (193)
35 l-thyroxin.tw. (417)
36 levothyroxin.tw. (139)
37 thyroxin.tw. (3273)
38 eltroxine.tw. (14)
39 or/24-38 (65149)
40 23 and 39 (1254)
41 Clinical Trial/ (962428)
42 Randomized Controlled Trial/ (479673)
43 exp randomization/ (76644)
44 Single Blind Procedure/ (30038)
45 Double Blind Procedure/ (142304)
46 Crossover Procedure/ (53731)
47 Placebo/ (302872)
48 Randomi?ed controlled trial$.tw. (170118)
49 Rct.tw. (26475)
50 random allocation.tw. (1711)
51 randomly allocated.tw. (28610)
52 allocated randomly.tw. (2271)
53 (allocated adj2 random).tw. (789)
54 Single blind$.tw. (20076)
55 Double blind$.tw. (177577)
56 ((treble or triple) adj blind$).tw. (726)
57 placebo$.tw. (259211)
58 prospective study/ (416492)
59 or/41-58 (1839556)
60 case study/ (51379)
61 case report.tw. (343137)
62 abstract report/ or letter/ (1013729)
63 or/60-62 (1400044)
64 59 not 63 (1792698)
65 40 and 64 (215)
1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (63828)
2 embryo$ transfer$.tw. (19552)
3 in vitro fertili?ation.tw. (28214)
4 icsi.tw. (15022)
5 intracytoplasmic sperm injection$.tw. (8926)
6 (blastocyst adj2 transfer$).tw. (2142)
7 ivf.tw. (37639)
8 exp infertility therapy/ or exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (91914)
9 assisted reproduct$.tw. (20782)
10 artificial insemination.tw. (5667)
11 iui.tw. (3027)
12 intrauterine insemination$.tw. (3525)
13 ovulation induc$.tw. (5367)
14 (ovari$ adj2 stimulat$).tw. (10314)
15 superovulat$.tw. (3684)

16 ovarian hyperstimulation.tw. (7074)
17 COH.tw. (2267)
18 infertil$.tw. (77808)
19 subfertil$.tw. (6467)
20 (ovari$ adj2 induction).tw. (321)
21 (euthyroid adj3 women).tw. (625)
22 (hypothyroid$ adj3 women).tw. (1008)
23 or/1-22 (178119)
24 exp thyroxine/ (42246)
25 Thyroxine.tw. (24726)
26 triiodothyronine.tw. (15000)
27 Levothyroxine.tw. (5674)
28 L-thyroxine.tw. (3107)
29 liotrix.tw. (4)
30 liothyronine.tw. (277)
31 Levothroid.tw. (110)
32 (Levoxyl or Synthroid or Unithroid).tw. (731)
33 Tetraiodothyronine.tw. (329)
34 eltroxin.tw. (214)
35 l-thyroxin.tw. (422)
36 levothyroxin.tw. (154)
37 thyroxin.tw. (2971)
38 eltroxine.tw. (14)
39 or/24-38 (61481)
40 23 and 39 (1358)
41 Clinical Trial/ (946460)
42 Randomized Controlled Trial/ (537168)
43 exp randomization/ (81722)
44 Single Blind Procedure/ (34474)
45 Double Blind Procedure/ (155781)
46 Crossover Procedure/ (58508)
47 Placebo/ (317612)
48 Randomi?ed controlled trial$.tw. (198013)
49 Rct.tw. (31589)
50 random allocation.tw. (1854)
51 randomly allocated.tw. (31839)
52 allocated randomly.tw. (2405)
53 (allocated adj2 random).tw. (798)
54 Single blind$.tw. (22274)
55 Double blind$.tw. (188762)
56 ((treble or triple) adj blind$).tw. (910)
57 placebo$.tw. (280295)
58 prospective study/ (506409)
59 or/41-58 (1994187)
60 case study/ (60058)
61 case report.tw. (365918)
62 abstract report/ or letter/ (1042482)
63 or/60-62 (1459189)
64 59 not 63 (1944289)
65 40 and 64 (231)

Appendix 5. PsycINFO search strategy

Ovid platform

Searched from 1806 to 8 April 2019

1 exp Infertility/ or exp Reproductive Technology/ (3322)
2 embryo transfer$.tw. (119)
3 vitro fertili?ation.tw. (710)
4 ivf.tw. (538)
5 icsi.tw. (70)

6 intracytoplasmic sperm injection$.tw. (54)
7 assisted reproduct$.tw. (892)
8 artificial insemination.tw. (253)
9 iui.tw. (35)
10 intrauterine insemination$.tw. (26)
11 ovulation induc$.tw. (30)
12 (ovari$ adj2 stimulat$).tw. (57)
13 superovulat$.tw. (6)
14 ovarian hyperstimulation.tw. (11)
15 COH.tw. (114)
16 infertil$.tw. (3345)
17 subfertil$.tw. (88)
18 (ovari$ adj2 induction).tw. (7)
19 (euthyroid adj5 women).tw. (16)
20 (hypothyroid$ and women).tw. (154)
21 or/1-20 (5510)
22 exp Thyroxine/ (357)
23 Thyroxine.tw. (916)
24 triiodothyronine.tw. (641)
25 Levothyroxine.tw. (158)
26 L-thyroxine.tw. (71)
27 eltroxin.tw. (1)
28 l-thyroxin.tw. (7)
29 thyroxin.tw. (142)
30 or/22-29 (1499)
31 21 and 30 (53)
32 random.tw. (54895)
33 control.tw. (422512)
34 double-blind.tw. (22033)
35 clinical trials/ (11285)
36 placebo/ (5225)
37 exp Treatment/ (711491)
38 or/32-37 (1124553)
39 31 and 38 (20)

Appendix 6. CINAHL search strategy

EBSCO platform

Searched from 1961 to 8 April 2019

#	Query	Results
S41	S26 AND S40	26
S40	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39	3,268
S39	TX levothyroxin	9
S38	TX eltroxin	7
S37	TX Tetraiodothyronine	25
S36	TX Levothroid	5
S35	TX L-thyroxine	128

(Continued)

S34	TX liothyronine	52
S33	TX (Levoxyl or Synthroid or Unithroid)	44
S32	TX l-thyroxin	12
S31	TX thyroxin	127
S30	TX Levothyroxine	598
S29	TX triiodothyronine	943
S28	TX Thyroxine	2,651
S27	(MM "Thyroxine+")	933
S26	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	19,877
S25	TX intra-uterine insemination	27
S24	TX coitus or TX subfertil* or TX infertile*	5,360
S23	(MM "Coitus")	997
S22	TX natural cycle*	346
S21	TX expectant management	871
S20	TX timed intercourse	36
S19	TX (ovari* N2 induction)	32
S18	TX COH	225
S17	TX ovarian hyperstimulation	787
S16	TX superovulat*	78
S15	TX ovulation induc*	1,645
S14	TX intrauterine insemination	444
S13	TX IUI	322
S12	TX artificial insemination	749
S11	TX assisted reproduct*	3,519
S10	(MM "Insemination, Artificial")	417
S9	(MM "Reproduction Techniques+")	8,395
S8	TX intracytoplasmic sperm injection*	822

(Continued)

S7	TX embryo* N3 transfer*	2,823
S6	TX ovar* N3 hyperstimulat*	792
S5	TX ovari* N3 stimulat*	914
S4	TX IVF or TX ICSI	4,611
S3	(MM "Fertilization in Vitro")	3,216
S2	TX vitro fertilization	6,520
S1	TX vitro fertilisation	6,520

CONTRIBUTIONS OF AUTHORS

MA (contact author): writing the protocol, literature search, study selection, data extraction, statistical analysis and drafting the review manuscript.

YS: drafting the protocol and expert advice on the review.

JB: drafting the protocol and developing search strategies. Providing expert advice on statistical analysis and results.

RA: expert advice on drafting of the protocol and review.

LC: literature search, study selection, data extraction, statistical analysis and advice on drafting of review manuscript.

DECLARATIONS OF INTEREST

MA: none known.

YS: none known.

JB: none known.

RA: none known.

LC: none known.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.
- Centre of Reproductive Medicine, University Hospitals Coventry & Warwickshire NHS Trust, UK.
- Department of Reproductive Endocrinology, Royal Free Hospital NHS Trust, London, UK.
- Department of Reproductive Medicine, St Marys Hospital, Central Manchester University Hospitals NHS Trust, UK.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

On the advice of Cochrane referees, we moved adverse effects of thyroxine to be our primary harms outcome. We also reported secondary outcomes of maternal pregnancy complications and foetal complications during pregnancy under adverse effects of thyroxine due to potential associations with thyroxine treatment.

We decided to report effect estimates using risk ratio (RR) rather than odds ratio (OR) as planned in our protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hormone Replacement Therapy [adverse effects]; Abortion, Spontaneous [epidemiology]; Autoimmune Diseases [*drug therapy]; Fertilization in Vitro; Hypothyroidism [blood] [*drug therapy]; Infertility, Female [*drug therapy]; Live Birth [epidemiology]; Pregnancy, Multiple; Randomized Controlled Trials as Topic; Reproductive Techniques, Assisted; Sperm Injections, Intracytoplasmic; Thyroid Diseases [blood] [*drug therapy]; Thyroid Gland [immunology]; Thyrotropin [blood]; Thyroxine [adverse effects] [blood] [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy