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Interventions for preventing and treating hyperthyroidism in pregnancy

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Abstract

Background—Women with hyperthyroidism in pregnancy have increased risks of miscarriage, stillbirth, preterm birth, and intrauterine growth restriction; and they can develop severe pre-eclampsia or placental abruption.

Objectives—To assess the effects of interventions for preventing or treating hyperthyroidism in pregnant women.

Search methods—We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (28 July 2010).

Selection criteria—We intended to include randomised controlled trials comparing antithyroid treatments in pregnant women with hyperthyroidism.

Data collection and analysis—Two review authors would have assessed trial eligibility and risk of bias, and extracted data.

Main results—No trials were located.

Authors' conclusions—As we did not identify any eligible trials, we are unable to comment on implications for practice, although early identification of hyperthyroidism before pregnancy may allow a woman to choose radioactive iodine therapy or surgery before planning to have a child. Designing and conducting a trial of antithyroid drugs for pregnant women with hyperthyroidism presents formidable challenges. Not only is hyperthyroidism a relatively rare condition, both of the two main drugs used have potential for harm, one for the mother and the

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CONTRIBUTIONS OF AUTHORS

Rachel Earl and Philippa Middleton drafted the protocol and review, with input from Caroline Crowther.

DECLARATIONS OF INTEREST

None known.

other for the child. More observational research is required about the potential harms of methimazole in early pregnancy and about the potential liver damage from propylthiouracil.

Medical Subject Headings (MeSH)

Hyperthyroidism [prevention & control *therapy]; Pregnancy Complications [prevention & control *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

BACKGROUND

Description of the condition

Hyperthyroidism is caused by an over-active thyroid gland, resulting in excessive release of thyroid hormones such as thyroxine (T₄) or triiodothyronine (T₃) (Abraham 2005; Mestman 2004; Polak 2004).

The prevalence of hyperthyroidism in pregnancy ranges from 0.1% to 0.4%, with Graves' disease accounting for 85% of these cases (Abalovich 2007; Mestman 2004). Graves' disease is an autoimmune disease defined as hyperthyroidism that is specifically caused by stimulation of the thyroid by thyrotrophin receptor stimulating antibodies (TRAb) (Marx 2008). Symptoms of Graves' disease include palpitations, heat intolerance, increased sweating, increased appetite, weight loss, insomnia, irritability, mood swings, frequent bowel movements, diarrhoea, pruritus, nervousness, hand tremor, decreased tolerance to exercise, shortness of breath and eye symptoms (frequent lacrimation, double vision, retro-orbital pain).

Graves' disease is more common in women than in men, and is most common in women aged between 20 and 40 years (Abraham 2005), which corresponds with women's peak reproductive years. About half the women who experience hyperemesis gravidarum (severe nausea and vomiting) have elevated T₄ concentrations, but there does not appear to be a direct link between hyperemesis gravidarum and thyroid function (LeBeau 2006).

Other, less common causes of hyperthyroidism in pregnancy include single toxic adenoma, toxic multinodular goitre (less than 5%) (Mestman 2004), subacute thyroiditis (thyroid inflammation), trophoblastic tumour or hydatidiform molar disease (a mass forming in the uterus) (Abalovich 2007; Palmieri 2005), iodine induced hyperthyroidism, struma ovarii (an ovarian tumour composed part or entirely of thyroid tissue; Papanikolaou 2007), or thyrotropin receptor activation (Marx 2008).

Transient gestational thyrotoxicosis (symptomatic or asymptomatic) can occur especially in the first trimester of pregnancy (Marx 2008), but usually resolves when human chorionic gonadotropin (HCG) concentrations decline; and treatment with antithyroid drugs is usually not necessary (LeBeau 2006) or effective in cases of HCG-induced hyperthyroidism (Girling 2006). The majority of women in remission from Graves' disease who become pregnant will

relapse postpartum or will develop postpartum thyroiditis (abnormal thyroid concentrations) (Cooper 2005).

Diagnosis of maternal hyperthyroidism—Most pregnant women with hyperthyroidism are diagnosed with thyroid disease prior to conception (Marx 2008; Mestman 2004) and will have previously received treatment for the condition. Women with stable Graves' disease may experience an exacerbation during early pregnancy, or women in remission may experience a relapse of Graves' disease (LeBeau 2006). New diagnoses of hyperthyroidism in pregnancy are uncommon, perhaps because untreated hyperthyroidism can be associated with infertility (Girling 2006).

Since radioactive iodine diagnostic tests are contraindicated during pregnancy (Marx 2008), other laboratory tests, coupled with careful history and physical examination, are used to diagnose hyperthyroidism (American Thyroid Association 2005). Diagnosing Graves' disease in pregnancy may be difficult as symptoms such as heat intolerance may part be of normal pregnancy. Women with Graves' disease may have a goitre (enlargement of the thyroid gland), but elevated T₄ and presence of thyroid autoantibodies (TRAb) usually confirm the diagnosis (LeBeau 2006).

Women who have pre-pregnancy ablation treatment for Graves' disease may need increased doses of thyroid replacement therapy soon after conception, or women with currently normal thyroid readings may have high concentrations of thyroid stimulating immunoglobulins, putting their fetuses at risk of developing hyperthyroidism (Mestman 2004).

Adverse maternal and pregnancy outcomes—Women with hyperthyroidism in pregnancy can develop severe pre-eclampsia or placental abruption. They have increased risks of miscarriage, stillbirth, preterm birth, and intrauterine growth restriction (Abalovich 2007; Casey 2007; LeBeau 2006; Marx 2008; Mestman 2004). Women with the poorest control of their hyperthyroidism have the highest risk of complications (LeBeau 2006).

Congestive heart failure can occur in 10% of untreated women, especially when cardiac demand is increased (for example, through exercise) (Mestman 2004; Sheffield 2004). Thyroid storm (thyrotoxic crisis or accelerated hyperthyroidism) is a rare but serious complication of hyperthyroidism. In a thyroid storm, women present severe symptoms of thyrotoxicosis such as hyperpyrexia (more than 39.4 °C), neuropsychiatric symptoms, tachycardia (pulse rate exceeding 140 beats/minute), nausea, vomiting, liver dysfunction, congestive heart failure (Mestman 2004), diarrhoea, dehydration, coma and delirium (Casey 2007). In pregnancy, thyroid storm can be precipitated by pre-eclampsia, induction of labour and placenta praevia (Mestman 2004).

In order to prevent fetal death or lifelong impairment, it is important to establish fetal thyroid status early in the pregnancy of a woman with Graves' disease (Polak 2004).

In women with Graves' disease, maternal antibodies (TRAb) can cross the placenta and stimulate the fetal thyroid (Mestman 2004), which may result in fetal tachycardia, intrauterine growth retardation, cardiac failure and fetal goitre (Marx 2008). This fetal

stimulation may rarely result in neonatal hyperthyroidism, with 2% to 5% of infants born to women with Graves' disease being affected (American Thyroid Association 2005).

Neonatal hyperthyroidism can occur even if a woman has already been treated for Graves' disease in the past and is receiving thyroxine therapy (Mestman 2004).

Description of the intervention

Of the three recognised treatment options for hyperthyroidism (radioiodine therapy, antithyroid drug therapy and surgery), generally only drug therapy is considered for treating pregnant women. Radioiodine treatment is contraindicated in pregnancy (Marx 2008) because it destroys the fetal thyroid gland, resulting in permanent hypothyroidism in the newborn (American Thyroid Association 2005; Casey 2007). Subtotal thyroidectomy is a treatment option in cases where serious adverse responses to antithyroid drug therapy are observed, where consistently high doses of antithyroid drugs are needed to control the hyperthyroidism or if the woman has not been able to adhere to antithyroid drug therapy (Abalovich 2007; Casey 2007).

Pregnant women with Graves' disease usually show remission in the third trimester, allowing them to stop taking antithyroid drugs, but if remission does not occur, then neonatal hyperthyroidism/thyrototoxicosis is more likely (Horsley 2007).

The main antithyroid drugs used in pregnancy are the thionamides, propylthiouracil (PTU), methimazole and carbimazole. PTU is currently the favoured drug for use in pregnancy, as it is associated with fewer teratogenic effects (*see below*) (Marx 2008). However, since there have been reports of liver damage in people taking PTU, it may be reasonable for pregnant hyperthyroid women to be treated with PTU in the first trimester (to reduce any teratogenic effects of methimazole) and then to change to methimazole (Cooper 2009).

Iodide drugs have rarely been used for hyperthyroidism during pregnancy due to reports of neonatal hypothyroidism (LeBeau 2006).

The beta-blocker, propranolol, may be used to relieve a woman's hyperthyroid symptoms (Abalovich 2007; Mestman 2004).

Maternal antithyroid drug treatment and teratogenicity—Congenital anomalies such as aplasia cutis (scalp lesions) and, very rarely, choanal atresia (blocked nasal passage) or oesophageal atresia have been reported with methimazole (Abalovich 2007; Cooper 2005).

Effects of maternal antithyroid drug treatment on the fetal thyroid; on the neonate; and long-term effects—The US Food and Drug Administration has classed both PTU and methimazole as being of risk to the fetus because of the potential for fetal hypothyroidism (Cooper 2005). For this reason, doses of antithyroid drug should be kept as low as possible and, once normal thyroid function has been achieved and symptoms stabilised, doses should be tapered down (Casey 2007; Cooper 2005; Marx 2008). The risk of fetal hypothyroidism is, however, negligible if maternal thyroxine is maintained at or

slightly above the upper limit of normal (Cooper 2005). Avoiding maternal overtreatment is important since fetal thyrotropin stimulation, goitre formation and possibly respiratory compromise after birth from tracheal compression may result (LeBeau 2006).

Neonatal hyperthyroidism may develop several days after birth in babies whose mothers were treated with antithyroid drugs, since the neonates no longer have the benefit of the in utero exposure to the medication (Mestman 2004).

Long-term effects of exposure to antithyroid drug in utero (especially on measures of IQ and psychomotor development) are potentially possible (LeBeau 2006) but have not been shown (Azizi 2002; Eisenstein 1992; Marx 2008).

Maternal adverse effects of antithyroid drug treatment: Up to 15% of women prescribed antithyroid drug therapy experience adverse effects such as itching, rash, hives, joint pain and swelling, fever, altered taste sensation, nausea and vomiting (Abraham 2005). Serious adverse effects such as agranulocytosis (a fall in white cell blood count), sepsis, abnormal liver function and vasculitis (inflammation of blood vessels) are rare (Abraham 2005; Casey 2007; Cooper 2005). Fever and sore throat are the most common presenting symptoms of agranulocytosis and women with these symptoms should cease their drug therapy and seek medical advice (Cooper 2005).

Maternal antithyroid drug treatment and lactation: Antithyroid drugs such as PTU and methimazole are secreted in breast milk and hence concerns have been raised about the safety of breastfeeding while undergoing antithyroid drug therapy (Marx 2008). Mestman 2004 suggests that breastfeeding by mothers with Graves' disease should be allowed when maternal daily doses of PTU are less than 150 to 200 mg/day or 10 mg/day of methimazole. The American Academy of Pediatrics has approved both PTU and methimazole for nursing mothers (American Academy of Pediatrics 2001).

Subclinical hyperthyroidism: Treatment of maternal subclinical hyperthyroidism has not been shown to improve pregnancy outcomes and may risk unnecessary exposure of the fetus to antithyroid drugs (Abalovich 2007; Casey 2007).

How the intervention might work

Thionamide drugs work by blocking the synthesis of thyroid production in the thyroid gland and may also help to control Graves' disease by indirectly influencing the immune system (Abraham 2005).

Why it is important to do this review

Rationale for review—A systematic review of trials evaluating interventions for preventing and treating hyperthyroidism in pregnant women will present the current evidence for averting maternal, fetal and neonatal adverse outcomes. This will allow women to make informed choices about managing their hyperthyroid condition during pregnancy.

OBJECTIVES

To assess the effects of interventions for preventing or treating hyperthyroidism in pregnant women.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials or quasi-randomised trials, including abstracts.

Types of participants—Women with hyperthyroidism, including:

- women diagnosed with hyperthyroidism for the first time during pregnancy;
- women on antithyroid therapy at the time of conception;
- women on remission from antithyroid therapy;
- previous history of ablation therapy for hyperthyroidism, either by surgery or by iodine 131.

Types of interventions—Any form of antithyroid therapy versus no therapy or comparisons of two forms of antithyroid therapy.

Types of outcome measures

Primary outcomes

Maternal

1. Overall clinical improvement in symptoms of hyperthyroidism (such as anxiety, tachycardia, heat intolerance, diarrhoea, palpitations, increased sweating, increased appetite, insomnia, irritability, mood swings, frequent bowel movements, pruritus, nervousness, hand tremor, decreased tolerance to exercise, shortness of breath, cardiac dysfunction, congestive heart failure, cardiac abnormality; ophthalmopathy (e.g. double vision, retro-orbital pain)).
2. Pre-eclampsia/pregnancy-induced hypertension.

Infant

1. Preterm birth.

Childhood

1. Neurodevelopmental disabilities.

Secondary outcomes

Maternal

1. Mode of birth.
2. Induction of labour.

3. Adverse effects (such as agranulocytosis, drug rash, abnormal liver function, vasculitis).
4. Weight change.
5. Postpartum thyroid dysfunction.
6. Thyroid antibody status (free T₄ concentrations, free thyroxine index (FT₄I)).
7. Health-related quality of life.
8. Mortality.
9. Miscarriage.
10. Placental abruption.

Fetal, neonatal, infant

1. Fetal, neonatal and postneonatal mortality.
2. Fetal thyroid function.
3. Congenital malformations.
4. Admission to intensive care nursery.
5. Neonatal hyperthyroidism.

Childhood

1. Attention deficit hyperactivity disorder.
2. Behavioural problems.

Search methods for identification of studies

Electronic searches—We contacted the Trials Search Co-ordinator who search the Cochrane Pregnancy and Childbirth Group's Trials Register (28 July 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies—In future updates, at least two review authors will independently assess for inclusion all the potential studies identified as a result of the search strategy, and we will resolve any disagreement through discussion or, if required, by consulting another person.

Data extraction and management—We designed a form to extract data. For studies eligible for future updates, at least two review authors will extract the data using the agreed form and we will resolve discrepancies through discussion or, if required, consult another person. We will enter data into Review Manager software (RevMan 2008) and check for accuracy. When information regarding any of the above was unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies—In future updates at least two review authors will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). We will resolve any disagreement by discussion or by involving another assessor.

(1) Sequence generation (checking for possible selection bias): For each study included in future updates, we will describe the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the methods as:

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

(2) Allocation concealment (checking for possible selection bias): For each study included in future updates, we will describe the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);

- unclear.

(3) Blinding (checking for possible performance bias): For each study included in future updates, we will describe all the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider studies to be at low risk of bias if they were blinded, or if we judge that lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations): For each study included in future updates, we will describe for each included study and for each outcome or class of outcomes the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- adequate;
- inadequate;
- unclear.

(5) Selective reporting bias: For each study included in future updates, we will describe how we investigated the possibility of selective outcome reporting bias and report what we find.

We will assess the methods as:

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

(6) Other sources of bias: For each study included in future updates, we will describe any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias: in future updates we will make explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2009). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider that it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

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

Continuous data: For continuous data, we will use mean difference with 95% confidence intervals if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

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

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

Assessment of heterogeneity—We will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if T^2 is greater than zero and either I^2 is greater than 30% or there is a low P-value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases—We will produce funnel plots if there are 10 or more trials in analyses. We will then perform a visual assessment of funnel plot asymmetry. We will perform exploratory analyses to investigate any suggestion of visual asymmetry in the funnel plots.

Data synthesis—We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that trials were examining the same intervention, and the trials' populations and methods are judged to be sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ among trials, or if we detect substantial statistical heterogeneity, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2 .

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses.

Subgroup analysis and investigation of heterogeneity—In future updates we plan to carry out the following subgroup analyses.

1. Reason for hyperthyroidism (Graves' disease versus other causes).
2. Treatment regimens (drug A versus drug B; high versus lower dose and shorter versus longer length of treatments).

We will use only primary outcomes in subgroup analysis.

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals will indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis—In future updates we will carry out sensitivity analyses to explore the effects of adequacy of allocation concealment (including quasirandomisation) and other risk of bias components.

We will use only primary outcomes in sensitivity analysis.

RESULTS

Description of studies

We did not identify any eligible trials.

Results of the search—We did not identify any eligible trials.

Included studies—We did not identify any eligible trials.

Excluded studies—We did not identify any eligible trials.

Risk of bias in included studies

We did not identify any eligible trials.

Effects of interventions

We did not identify any eligible trials.

DISCUSSION

Pregnant women with hyperthyroidism are faced with the dilemma of “choosing between a drug associated with small risk of fetal birth defects and another drug associated with a similarly small but finite risk of serious liver injury in the mother” (Cooper 2009). As there is no evidence from trials to guide a choice between propylthiouracil (PTU) and then switching to methimazole, or staying with PTU, Cooper 2009 emphasises the need to offer hyperthyroid women radioactive iodine therapy or surgery before they plan to become pregnant.

In any woman of reproductive age with hyperthyroidism, prepregnancy counselling and management to control the disease are paramount (Mestman 2004).

AUTHORS' CONCLUSIONS

Implications for practice

As we did not identify any eligible trials, we are unable to comment on implications for practice, although early identification of hyperthyroidism before pregnancy may allow a woman to choose radioactive iodine therapy or surgery before planning to have a child.

Implications for research

Designing and conducting a trial of antithyroid drugs for pregnant women with hyperthyroidism presents formidable challenges. Not only is hyperthyroidism a relatively rare condition, both of the two main drugs used have potential for harm, one for the mother and the other for the child.

More observational research is required about the potential harms of methimazole in early pregnancy and about the potential liver damage from propylthiouracil.

Acknowledgments

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

SOURCES OF SUPPORT

Internal sources

- ARCH, Robinson Institute, The University of Adelaide, Australia.

External sources

- Australian Department of Health and Ageing, Australia.

DATA AND ANALYSES

This review has no analyses.

HISTORY

Protocol first published: Issue 8, 2010

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* *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

No evidence located from randomised trials for drugs to treat pregnant women with hyperthyroidism

Hyperthyroidism in pregnancy is a rare, serious condition which can increase the risks of miscarriage, stillbirth, preterm birth, and intrauterine growth restriction. Pregnant women who are hyperthyroid may also develop severe pre-eclampsia or placental abruption. Most of these women have Graves' disease, an autoimmune disease most common in women aged 20 to 40 years. Most pregnant women with hyperthyroidism are diagnosed with thyroid disease prior to conception and will have previously received treatment for the condition. Generally only drug therapy is considered for treating pregnant women with hyperthyroidism. Radioiodine treatment is not used in pregnancy because it destroys the fetal thyroid gland, resulting in permanent hypothyroidism in the newborn.

The main antithyroid drugs used are the thionamides, propylthiouracil (PTU), methimazole and carbimazole. PTU is currently the favoured drug for use in pregnancy, as it is associated with fewer teratogenic effects (scalp lesions) than methimazole. However, since there have been reports of liver damage in people taking PTU, it may be reasonable for pregnant hyperthyroid women to be treated with PTU in the first trimester (to reduce any teratogenic effects of methimazole) and then to change to methimazole.

We could not identify any randomised trials to help inform women and their doctors about which antithyroid drugs are most effective, with the lowest potential for harm.