DRAFT REPORT

Cost-effectiveness of strategies to prevent adverse obstetrical outcomes from thyroid dysfunction in pregnant women

Economic evaluation to support national evidence based antenatal care guidelines

Prepared for
Department of Health and Ageing

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THE CENTRE FOR INTERNATIONAL ECONOMICS
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Summary

The potential clinical outcomes and impact of subclinical thyroid dysfunction during pregnancy have been the subject of much debate.

Where (limited) evidence exists, adverse clinical outcomes are limited to hyperthyroidism and hypothyroidism if overt, or subclinical when TPO antibodies are present.

At this stage, there is not enough clinical evidence so show that treatment reduces adverse obstetrical and neonatal outcomes, and there are no economic evaluations relevant to Australia that enable an assessment of the impact of a potential routine screening program for thyroid dysfunction to detect women with hypothyroidism that have not already been diagnosed.

The additional clinical evidence required for a complete economic evaluation includes adverse outcomes caused by subclinical hypothyroidism, the effectiveness of thyroxine replacement therapy in improving these outcomes, and the accuracy of the tests.

Hence there needs to be robust evidence that treatment works, and that any benefits can be attributed to the scan in order for a complete economic evaluation to be undertaken.

The benefits of universal screening would lie in the advantages of being able to identify and treat women with subclinical disease or overt hypothyroidism with minor symptoms developed during pregnancy.

The alternative that is currently recommended is to only test women with distinct risk factors for thyroid dysfunction in the first trimester, including:

- personal or family history of thyroid dysfunction
- presence of goitre
- presence of thyroid autoantibodies
- symptoms of clinical signs suggestive of thyroid dysfunction including anaemia and elevated cholesterol
- type 1 diabetes or other autoimmune disease, or
- history of miscarriage or preterm birth.[1]

[1] Abalovich, M. Amino, N, Barbour, L. Cobin, R. De Groot, L. Glinoer, D. Mandel, S. and Stagnaro-Green, S, 2007, Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metabolism, 92(8) as cited in the Post-consultation draft of the Clinical Practice Guidelines Antenatal Care Module II recommendations by the Department of Health and Ageing.

Hence the two strategies examined in this evaluation include a risk based approach to screening (only offered when symptoms of high risk of thyroid dysfunction are present), and routine screening (universal testing within the first trimester).

The resources used in a screening strategy include the costs of screening (testing, staff time and materials) and treatment with thyroxine replacement therapy. The potential health outcomes identified for each clinical option include preterm birth, miscarriages and postpartum thyroiditis (PPT). A number of outcomes that would be difficult to quantify include the impact of excessive thyroxine treatment and maternal stress from test results.

A review of the economic literature revealed few studies that assessed the cost-effectiveness of the strategies, and none were wholly relevant to the study question or the Australian context.

Key findings of this study

This report provides the groundwork for evaluating the strategies in light of the current evidence.

It highlights the main data gaps that need to be filled before a more fulsome economic evaluation can be performed.

The key findings from this review include that:

- there are no relevant Australian economic evaluations in the literature that are directly relevant to this review
- there is uncertainty surrounding key parameters that must be addressed before a robust economic evaluation can be performed
- the clinical evidence required for a fulsome economic evaluation includes data on:
  - adverse outcomes caused by subclinical hypothyroidism and adverse obstetrical and neonatal outcomes
  - the effectiveness of thyroxine replacement therapy in improving on hypothyroid pregnant women and the associated reduction in adverse obstetrical and neonatal outcomes, and
  - the accuracy of the tests that use pregnancy specific ranges relevant to the population that may be influenced by iodine deficiency on the population.

2 Background

Evidence on the adverse clinical outcomes associated with thyroid dysfunction are limited to hyperthyroidism and hypothyroidism if overt or subclinical when TPO antibodies are present.

Given existing treatment guidelines for hyperthyroidism, screening is only relevant for the forms of hypothyroidism mentioned above.

Causes and treatments for thyroid dysfunction in pregnant women

Thyroid dysfunction in the form of hypothyroidism is estimated to occur in 2 to 3 per cent of pregnant women.[2]

In adults, the thyroid produces hormones with functions in metabolism, and for children these hormones are essential for growth and development. The thyroid stimulating hormone (TSH) is responsible for the production of hormones thyroxine (T4) and triiodothyronine (T3). The fetus is dependent on the transplacental transfer of maternal T4 for neurological development, and it is normal for pregnant women to have lower levels of TSH for the corresponding production of T4 to meet fetal needs.[3] There are also measurement issues that can complicate what are 'normal' TSH levels for pregnant women (see box 2.1).

When thyroid dysfunction occurs, it is possible that adverse obstetrical outcomes can result, depending on the type of thyroid condition.

The two main types of thyroid dysfunction include:

- hyperthyroidism (overactive thyroid), normally caused by Graves' disease which is an autoimmune condition but also related to excess exposure to iodine and gestational thyrotoxicosis, and
- hypothyroidism (underactive thyroid), which is relatively more common in pregnancy (0.2 to 1 per cent with overt and 1.5 to 4 per cent with subclinical hypothyroidism) most commonly caused by the autoimmune disease, Hashimoto's disease or iodine deficiency.[4]

[2] Negro, R. Mestman, J. H. 2011. Thyroid disease in pregnancy, Best practice & research clinical endocrinology & metabolism, 25(6).

[3] Forehan, S. 2012, Thyroid disease in the perinatal period, Australian Family Physician, 41(8).

[4] Negro, R. Mestman, J. H. 2011, op. cit.

2.1 Differing TSH levels between pregnant and non-pregnant women

It is known that TSH levels are lower in pregnant than non-pregnant women. There has been a lack of consensus for these values due to multiple studies producing inconsistent results, which may be due to differing populations and iodine levels in the population.[5] However, guidelines including RANZCOG C-Obs 46 have provided sample trimester-specific reference intervals from serum TSH.[6]

Overall, standard laboratory reference ranges are not suitable for this testing as it leads to the under diagnosis of hypothyroidism and over diagnosis of hyperthyroidism. This would consequently lead to the excessive use of anti-thyroid therapy and inadequate care for hypothyroid women.

There is also evidence of inter assay variation for the measurement of free T4 immunoassays.[7] This has led to some concern over using free T4 testing in pregnancy to assess thyroid dysfunction.

Treatments differ depending on the type of thyroid dysfunction and diseases present (table 2.2).

By and large, *hyperthyroidism* is not screened for in pregnant women as preventative treatments are offered based on underlying diseases.

For instance, women with Graves' disease are typically diagnosed and treated with antithyroid medication prior to conception.[8]

Women with gestational transient thyrotoxicosis experience a self-limiting hyperthyroid state that does not usually require antithyroid medication.

This is not the case with respect to *hypothyroidism* in pregnancy, when testing is the most typical method used to diagnose the condition and distinguish between the type of hypothyroidism which impacts on the appropriate treatment course (treatment with thyroxine replacement therapy for overt hypothyroidism or subclinical hypothyroidism when women test positive for the thyroid peroxidase antibody (anti-TPO ab)).

No treatments are recommended for women who are euthyroid or have subclinical hypothyroidism if the anti-TPO test is negative.

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5 Gilbert, R. M. Hadlow, N.C. Walsh, J.P. Fletcher, S. J. Brown, S. J. Stuckey, B. G and Mun Lim, E. 2008, Assessment of thyroid function during pregnancy: first-trimester (weeks 9-13) reference intervals derived from Western Australian women. Medical Journal Australia, 189(5).

6 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, July 2012, C-Obs 46: Testing of serum TSH levels in pregnant women.

7 Anckaert, E. Poppe, K. Van Uytfanghe, K.et al. 2010. FT4 immunoassays may display a pattern during pregnancy similar to the equilibrium dialysis ID-LC/tandem MS candidate reference measurement procedure in site of susceptibility towards protein alterations. Clinica Chimica Acta, 411.

8 Forehan, S. 2012, op. cit.

This is in line with the treatment recommendations in the current guidelines by the Royal Australia and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), which recommends giving thyroxine replacement therapy when:

- a woman has overt hypothyroidism, and
- a woman has subclinical hypothyroidism and is anti-TPO antibody positive.[9]

2.2 Type of thyroid states, obstetrical outcome and treatment

States of thyroid function	Symptoms to the mother	Associated adverse obstetrical outcome if untreated[a]	Treatment
Euthyroid (normal functioning)	None	None	None
Hyperthyroidism	▪ Weight loss ▪ Heat tolerance ▪ Hypertension	Thyroid dysfunction in neonate, congenital malformations, miscarriage, preeclampsia, premature birth	Antithyroid therapy (propylthiouracil in first trimester, followed by methimazole or carbimazole after first trimester)
Overt hypothyroidism	▪ Weight gain ▪ Sensitivity to cold and dry skin	Miscarriage, premature birth, stillbirth	Thyroxine replacement therapy
Subclinical hypothyroidism	Few or no symptoms	Miscarriage, impaired neurodevelopment (contentious)	Not recommended if anti-TPO ab is negative, if positive treat with thyroxine replacement therapy[1]

Source: Mestman, J. H, 2012, Hypothyroidism in pregnancy, Curr Opin Endocrinol Diabetes Obes. 19(5). [1]The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, July 2012, C-Obs 46: Testing of serum TSH levels in pregnant women.

Supporting clinical evidence

There is some clinical evidence to support the use of thyroxine replacement therapy to return pregnant women with overt hypothyroidism to a euthyroid state. There is insufficient evidence that subclinical hypothyroid has an impact on obstetrical outcomes, hence no support for thyroxine replacement if there are no TPO antibodies.[10]

A recent Cochrane review by Reid, 2013 on the impact of treating hypothyroidism in pregnancy found:

> 'no difference between levothyroxine [thyroxine replacement] therapy and a control for treating pregnant euthyroid women with thyroid peroxidase antibodies for the outcome of pre-eclampsia, however a reduction in preterm birth and a trend towards reduced miscarriage with levothyroxine was shown. This review also showed no difference for pre-eclampsia or preterm birth when selenium was compared with placebo, however a promising reduction in postpartum thyroiditis was shown. Childhood neurodevelopmental delay was not assessed by any trial included in the review'[11]

Thus, the adverse outcomes of preterm birth, miscarriage and PPT are of interest.

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[9] The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (2012) op. cit.

[10] Ibid.

[11] Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. Cochrane Database Syst Rev. 2013 May 31(5).

Thyroid function screening

There has been debate regarding the need to screen women for thyroid dysfunction.

The function level of a thyroid can be determined in pregnant women through a series of blood tests which measure:

- TSH levels
- free T4 (FT4) levels, and
- antibodies against TPO.

This test is performed in the first trimester of pregnancy and if a woman is tested positive, an endocrinologist will review treatment options.

The aim of the treatment is to return the maternal thyroid to a euthyroid state and to ensure that the fetus is able to receive adequate maternal T4.

If overt hypothyroidism is identified, then thyroxine replacement therapy is given to the mother, followed by regular testing of TSH and T4 levels (every four to six weeks).[12]

If subclinical hypothyroidism is identified, then thyroxine therapy is given to the mother (if anti-TPO ab positive), followed by regular testing of TSH and T4 levels (every four to six weeks).[13]

The regular monitoring of TSH and T4 levels is used to titrate the thyroxine replacement therapy, that is, as levels become normalised, then women should receive less medication.

2.3 Testing and treatment algorithm for hypothyroidism in pregnant women

TSH	Free T4	Anti-TPO	Thyroid state	Treatment
High TSH	Low T4	Positive	Overt hypothyroidism (Hashimoto's disease)	Yes, thyroxine replacement
High TSH	Low T4	Negative	Overt hypothyroidism	Yes, thyroxine replacement
High TSH	Normal T4	Positive	Subclinical hypothyroidism	Yes, thyroxine replacement
High TSH	Normal T4	Negative	Subclinical hypothyroidism	No
Normal TSH	Normal T4	Negative	Euthyroid	No

Source: The CIE and The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, July 2012, C-Obs 46: Testing of serum TSH levels in pregnant women.

12 Stagnaro-Green, A. Abalovich, M. Alexander, E. et al. 2011. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum, Thyroid, 21(10).

13 Ibid.

Overview of the economic literature

There are very few economic evaluations on the cost-effectiveness of various screening strategies. See Appendix for the search strategy for the literature review of economic evaluations, along with findings of the critical appraisals.

The literature did not reveal any Australian economic studies of thyroid function testing. Although there were some international economic studies, none were wholly relevant to this evaluation. These include:

- Dosiou, et al. 2012, Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women.
  - A cost-utility analysis comparing different thyroid function screening strategies on the measured outcomes preterm birth, miscarriages and PPT. The authors found that either a risk-based or universal screening strategy was more cost-effective than no screening, whilst, risk-based screening has a lower cost-effective ratio compared to universal screening in an American setting. This study compared the most relevant interventions, comparators and outcomes to this study question, hence a number of inputs and variables were collected. This was the only study that utilised effectiveness of levothyroxine data from RCTs. However, the effectiveness data may not be transferable as Italy is characterised by moderate iodine deficiency.
- Thung, et al. 2009, The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism.
  - A cost-utility analysis comparing universal screening to no screening for thyroid dysfunction on the reduction of low child IQ in the U.S. The authors did not include a risk-based screening strategy comparator and found that universal screening was dominant compared to the no screening strategy. There were issues with the measurement and valuation of utilities for IQ and on the effectiveness of therapy.
- Dosiou, et al. 2008, Screening pregnant women for autoimmune thyroid disease: a cost-effectiveness analysis.
  - A cost-utility analysis comparing universal screening of first trimester TSH or anti-TPO testing compared to no screening of autoimmune thyroid dysfunction in the U.S. There was no risk-based screening comparator, the measured outcomes included PPT, gestational hypertension and low child IQ. There were issues with the valuation of utilities and the effectiveness of the therapy was not included. The authors found that universal screening was cost-effective compared to no screening.
- Bonds, et al. 2001, Cost-effectiveness of prenatal screening for postpartum thyroiditis.
  - A cost-utility analysis comparing universal screening of anti-TPO ab in first trimester, TSH at 6 weeks postpartum or no screening to detect PPT in the American setting. There were issues of the valuation of utilities, no details of effectiveness of therapy and no risk-based comparator. The authors found that universal screening of TSH at 6 weeks postpartum was the most cost-effective strategy. Sensitivity analysis revealed that the cost-effectiveness results were most sensitive to test characteristics including sensitivity, specificity and the costs of tests.

Key limitations in the literature

Existing economic evaluations require further clinical studies to be performed to assess the relevant measured outcomes and effectiveness of interventions. The gaps in the literature that prevent a more fulsome economic evaluation mainly relate to:

- the evidence surrounding subclinical hypothyroidism and adverse obstetrical and neonatal outcomes
- the evidence surrounding the accuracy of testing, that is, use of pregnancy specific ranges relevant to the population (may be influenced by iodine deficiency on the population), and
- the evidence regarding the effectiveness of thyroxine replacement therapy on hypothyroid pregnant women and the associated reduction in adverse obstetrical and neonatal outcomes.

3 Economic framework

The alternative options to routine screening are screening based on distinct risk factors or no screening at all.

The resources used in a screening strategy include the costs of screening (testing, staff time and materials) and treatment with thyroxine replacement therapy. The potential health outcomes identified for each clinical option include preterm birth, miscarriages and PPT.

A number of outcomes that would be difficult to quantify include the impact of excessive thyroxine treatment and maternal stress from test results.

Alternative strategies for detection and prevention of thyroid dysfunction in pregnancy

Option 1: Current recommendation of a risk-based approach to screening

Recommendations in the post-consultation draft Clinical Practice Guidelines Antenatal Care Module II are to adopt a risk-based approach to screening of thyroid function in pregnant women as follows:

- 'Do not routinely offer pregnant women thyroid function screening (Grade B)'
- 'Offer screening to pregnant women who have symptoms or high risk of thyroid dysfunction (Grade B)'

In risk-based screening, unless already diagnosed only women who exhibit symptoms or are considered at a high risk of having thyroid dysfunction are tested. Risk factors include:

- personal or family history of thyroid dysfunction
- presence of goitre
- presence of thyroid autoantibodies
- symptoms of clinical signs suggestive of thyroid dysfunction including anaemia and elevated cholesterol
- type 1 diabetes or other autoimmune disease, or
- history of miscarriage or preterm birth.[14]

[14] Abalovich, M. Amino, N, Barbour, L. Cobin, R. De Groot, L. Glinoer, D. Mandel, S. and Stagnaro-Green, S, 2007, op. cit.

Under this option, women with these risk factors would be recommended to have their thyroid function tested to determine whether they have hypothyroidism (overt or subclinical) within the first trimester, preferably at the first visit (first visit for antenatal care after confirmation of pregnancy).

Regular monitoring of thyroid function throughout pregnancy would then be standard for women after identifying abnormal levels.

The risk-based approach is the approach currently used in Australia, although there are some advocates for universal screening.[15]

Option 2: Universal testing of thyroid function in pregnant women

A clinical alternative to the risk-based approach is to offer routine or universal thyroid function testing in pregnant women during the first trimester.

In the universal or routine screening approach, all women would be tested within the first trimester, preferably at the first visit.

This option would be expected to identify more women with thyroid dysfunction, compared to the risk-based approach.

Universal screening would be expected to result in increased thyroxine therapy and may improve obstetrical outcomes.

Universal screening is not recommended by RANZCOG or the American Thyroid Association.[16]

Option 3: No screening of thyroid function in pregnant women

The no screening option is used to measure the impact of the above two options. It is unlikely that an Australian institution would adopt this approach, as it is current practice to have risk-based screening.

Costs and consequences of alternative options

Most of the costs and consequences of risk-based screening or universal screening (relative to no screening) are the same, although they differ in terms of the orders of magnitude involved (see table 3.1). For instance, universal screening involves increased costs of screening, and subsequently increase the number of women under thyroxine replacement therapy.

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15 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, July 2012, C-Obs 46: Testing of serum TSH levels in pregnant women.

16 Stagnaro-Green, Abalovich, M. Alexander, E. et al. 2011. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum, Thyroid, 21(10).

Risk-based screening does also require the cost of work-up for unscreened women (that is, eventual diagnosis and treatment), although these costs are minimal given women with subclinical disease would generally have no symptoms to prompt a diagnosis.

3.1 Costs and consequences of risk-based or universal thyroid function testing

Item	Risk-based screening	Routine screening	No screening
Cost (resource use)			
Cost of screening: ▪ cost of consultation with midwife ▪ first, second and third trimester for TSH levels, free T4 levels and anti-TPO antibody ▪ cost of analysis by pathology unit ▪ cost of consultation with endocrinologist if positive result	✓	✓	×
Cost of thyroxine replacement therapy and consultation	✓	✓	×
Cost of work-up (eventual diagnosis) of women with hypothyroidism	×	×	✓
Consequences (health outcomes)			
Measured health outcome			
Miscarriage	✓	✓	✓
Preterm birth	✓	✓	✓
Postpartum thyroiditis (PPT)	✓	✓	✓
Other health outcomes			
Preeclampsia	✓	✓	✓
Permanent states of thyroid dysfunction due to PPT	✓	✓	✓
Impacts on child IQ	✓	✓	✓
Emotional/psychological impacts on women	✓	×	×
Excessive exposure to thyroxine replacement therapy	✓	×	×

Source: The CIE

4 Early stage evaluation of alternative strategies

Decision trees were developed for the alternative clinical options along with assumptions.

There is lack of robust clinical evidence supporting the need to screen for subclinical hypothyroidism and these concerns are highlighted.

Data inputs were collected from the scientific literature regarding the prevalence of disease and potential effectiveness of thyroxine in subclinical patients in reducing miscarriages and preterm birth. The cost of screening and treatment from the Australian perspective were calculated using MBS and PBS data.

Defining the economic question

To help identify the most appropriate recommendation for antenatal care with respect to thyroid dysfunction, the key economic questions include:

- What is the relative cost-effectiveness in identifying and treating pregnant women with thyroid dysfunction through universal screening, risk-based screening or no screening?
  - What are the resource costs associated with each option?
  - What are the health outcomes associated with each option?

To answer this question, it is important to clearly set out the patient experience under each of these options — the interventions received under different circumstances, and the impact of these interventions on mother and fetus.

This has been done by developing clinical event pathways for each of the screening options. The respective options involve different (and some similar) costs and consequences which determine the probabilities of clinical events and their associated costs. These pathways are mapped out in chart 4.1. The intervention is thyroxine replacement therapy, and this is based on a positive result from the thyroid function tests.

The decision trees are read from left to right, a women is either hypothyroid or euthyroid, and the clinical option chosen will influence the number and magnitude of adverse obstetrical outcomes in women.

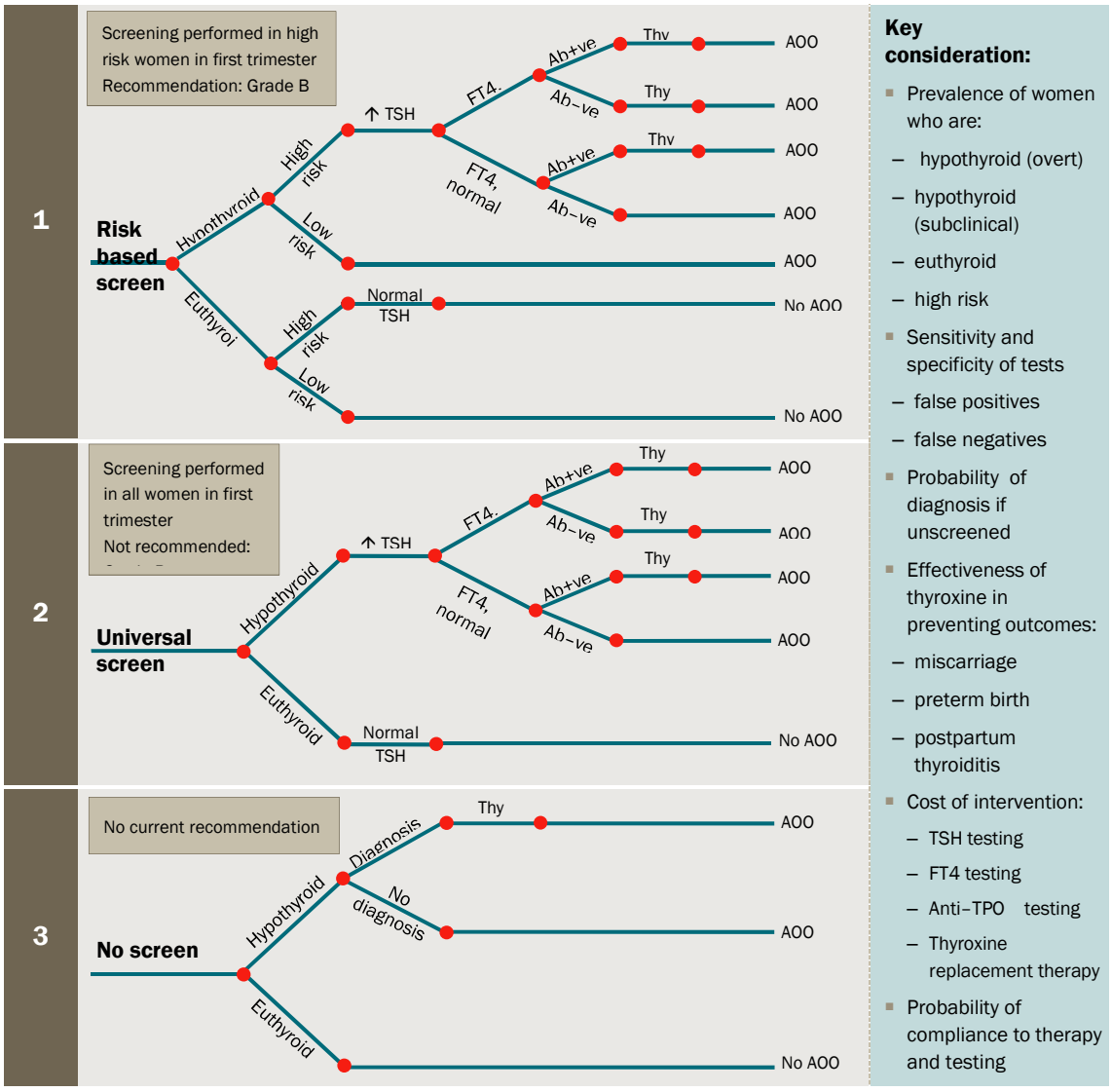
Under the risk-based screening strategy, women who are considered having high risk factors are tested (TSH, FT4 and anti-TPO ab). If they have low FT4 levels they are given thyroxine replacement therapy as this is diagnosed as overt hypothyroidism. If FT4 results are normal, women are diagnosed as being subclinical hypothyroid and are given thyroxine replacement therapy if they have TPO antibodies. Subsequently, women with no risk factors are not tested or treated.

Under the routine screening approach, all women have their TSH levels tested, women who are hypothyroid are further tested for FT4 levels and TPO antibodies and treated with thyroxine replacement therapy accordingly. Women who have normal TSH levels are not further tested or treated.

Under the no screening approach, no woman is screened, however a small number of women may be diagnosed and treated if they present with symptoms.

The clinical event pathways developed for this evaluation make various assumptions about risk factors and adoption of different strategies and associated outcomes. These are set out in box 4.2.

4.1 Alternative prevention strategies to address adverse obstetrical outcomes from thyroid dysfunction in pregnant women



Data source: The CIE

Key

TSH	*Thyroid stimulating hormone*	**Ab+ve**	*anti-TPO antibody positive*	**Thy**	*Thyroxine replacement therapy*
FT4	*Thyroxine*	**Ab-ve**	*anti-TPO antibody negative*	**AOO**	*Adverse obstetrical outcomes*

4.2 Assumptions underpinning alternative screening strategies

- Under risk-based screening only women who present with risk factors are tested for thyroid dysfunction.
- For subclinical hypothyroid women, only those that are anti-TPO ab positive are given thyroxine replacement therapy.
- The measured outcomes are adverse obstetrical outcomes that could include preterm birth, miscarriage and PPT.
- Under the no screening strategy it is possible that some women who present with symptoms of hypothyroidism will be tested and treated.
- The model requires parameters for the sensitivity and specificity for TSH, FT4 and anti-TPO tests. This would ultimately affect the detection rate as well as proportion of women who are treated.
- The model requires a parameter on compliance to daily dosing of thyroxine replacement therapy, if compliance to thyroxine replacement therapy is less than 100 per cent, than this would reduce the effectiveness of the therapy in reducing adverse obstetrical outcomes.

Understanding the economic impact of alternative strategies

Parameters of prevalence of disease and probabilities of events

Table 4.3 highlights concerns regarding some parameters for the model. There is uncertainty and a lack of evidence in a number of parameters, particularly, which adverse obstetrical outcomes are caused by subclinical hypothyroidism and if treatment is effective. Hence, the following information is required before the cost-effectiveness of strategies can be modelled.

4.3 The evidence and considerations for the parameters in the model

Parameter	Evidence and considerations
What is the prevalence of overt and subclinical hypothyroidism?	This figure is dependent on whether or not studies have utilised pregnancy specific reference ranges, and if the upper limits on these ranges are correct. Standard laboratory references would underestimate the number of women with hypothyroidism as the TSH level in pregnancy is lowered. The prevalence of overt hypothyroidism is likely to be more than 0.3 per cent considering this is the pooled prevalence from studies using high TSH upper limits.[1] Further, it is necessary to understand what proportion of women with overt hypothyroidism would be treated prior to conception.
Which adverse obstetrical and neonatal outcomes are linked to thyroid dysfunction?	There is some evidence to suggest hypothyroidism in pregnancy is linked to miscarriage, preterm birth, and PPT.[2] What evidence supports preeclampsia, gestational hypertension and childhood IQ? How should these outcomes be measured, how should utilities for different health outcomes be calculated? There are two RCTs performed in Italy that review the effectiveness of thyroxine replacement therapy on the reduction of a range of adverse outcomes. Of the four economic evaluations included for review, Dosiou, 2012 utilised the effectiveness data from these two studies.[3] Thung, 2009 and Dosiou, 2008 based their economic evaluations on observational data, in particular, the findings by Haddow et al, on thyroxine replacement therapy on child IQ.[4]

Parameter	Evidence and considerations
Are testing methods accurate for the detection of overt and subclinical hypothyroidism?	There is evidence of increasing use of pregnancy specific TSH levels in Australia.[5] Is the level of hypothyroidism in Australia related to inadequate iodine levels, autoimmune thyroid disease (anti-TPO etc.), or other risk factors? What are the issues relating to sensitivity and specificity of FT4 testing?
What is the probability of compliance in thyroxine replacement therapy?	Thung, 2009 and Dosiou, 2008 included compliance rates to thyroxine replacement therapy of 79 and 90 per cent respectively. What are the impacts of compliance on effectiveness of therapy?
Is thyroxine replacement therapy a safe and effective solution for pregnant women with hypothyroidism?	Is thyroxine replacement therapy effective in maintaining thyroid levels, such as TSH at adequate levels? Does thyroxine replacement therapy reduce the incidence of adverse obstetrical and neonatal outcomes? If so, what are they? Will thyroxine replacement therapy affect incidence and impacts of PPT on the women? Are there any adverse reactions associated with thyroxine replacement therapy?
How many cases of hypothyroidism can be detected with risk-based screening?	What proportion of hypothyroid pregnant women are likely to have the risk factors as listed in the Department's post-consultation draft Clinical Practice Guidelines Antenatal Care Module II list of risk factors in Australia compared to euthyroid women?
What is the expected dosage rate for women with hypothyroidism?	It has been suggested that treatment of 100 to 200mg per day of thyroxine for the duration of pregnancy is adequate. How is this expected to vary throughout pregnancy?

Note: anti-TPO ab = anti thyroid peroxidase antibody, FT4 = free thyroxine, IQ = intelligence quotient, PPT =postpartum thyroiditis and TSH = thyroid stimulating hormone

Source: [1]Stagnaro-Green A. 2011, Overt hyperthyroidism and hypothyroidism during pregnancy. Clin Obstet Gynecol. 2011 Sep; 54(3):478-87. [2]Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. 2013, Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy, Cochrane Database Syst Rev, 31(5). [3]Negro, R. Formoso, G. Mangieri, T. Pezzarossa, A. Dazzi, D. and Hassan, H. 2006. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: Effects on obstetrical complications. The Journal of Clinical Endocrinology & Metabolism, 91(7). Negro, R. Schwartz, A. Gismondi, R. Tinelli, A. Mangieri, T. Stagnaro-Green, A. 2010. Universal screening vs. case finding for detection and treatment of thyroid dysfunction during pregancy, J Clin Endocrinol Metabl, 9 (4). [4]Haddow, J. E. Palomaki, G. E. Allan, W. C. Williams, J. R. Knight, G. J. Gagnon, J. O'Heir, C. E. Mitchell, M. Hermos, R. J. Waisbren, S. E. Faix, J. D. and Klein, R. Z. 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child, The New England Journal of Medicine, 341(8). Gilbert, R. M. Hadlow, N.C. Walsh, J.P. Fletcher, S. J. Brown, S. J. Stuckey, B. G and Mun Lim, E. 2008, Assessment of thyroid function during pregnancy: first-trimester (weeks 9-13) reference intervals derived from Western Australian women. Medical Journal Australia, 189(5).

Table 4.4 highlights the available data on inputs in the model with respect of prevalence of disease and effectiveness of treatment.

4.4 Parameters for model, prevalence of disease and effectiveness of treatment

Item	Range/Value	Reference
Prevalence of overt hypothyroidism	0.001-1 per cent	Abalovich, 2002. Haddow, 2000. Mitchell, 2003. Casey, 2005. Vaidya, 2007. Negro, 2011. Dosiou, 2012.
Prevalence of subclinical hypothyroidism	1.5-4 per cent	Abalovich, 2002. Haddow, 2000. Mitchell, 2003. Casey, 2005. Vaidya, 2007. Negro, 2011. Dosiou, 2012
Prevalence of high risk factors in a population	19.9-26.5 per cent	Negro, 2010. Vaidya, 2007. Dosiou, 2012
Probability of having anti-TPO ab if overt hypothyroid	80 per cent	Allan, 2000
Probability of having anti-TPO ab if subclinical hypothyroid	50-60 per cent	Lazarus, 2010. Stagnaro-Green, 2011

Item	Range/Value	Reference
Effectiveness of levothyroxine replacement therapy in reducing preterm births	▪ 22.4 per cent have a preterm birth if anti-TPO ab positive and untreated. ▪ 7 per cent have a preterm birth if anti-TPO ab positive and treated with thyroxine ▪ Relative risk of preterm birth without levothyroxine therapy of 1.66	Negro, 2006
Effectiveness of levothyroxine replacement therapy in reducing miscarriages	▪ 13.8 per cent have a miscarriage if anti-TPO ab positive and untreated. ▪ 3.5 per cent have a miscarriage if anti-TPO ab positive and treated with thyroxine ▪ Relative risk of preterm birth without levothyroxine therapy of 1.72	Negro, 2006
Effectiveness of levothyroxine replacement therapy in reducing preterm births	▪ 16.3 per cent have a preterm birth if TSH>2.5, anti-TPO ab positive and untreated ▪ 4.8 per cent have a preterm birth if TSH>2.5, anti-TPO ab positive and treated with thyroxine	Dosiou, 2012 citing Negro, 2006. Negro, 2007.
Effectiveness of levothyroxine replacement therapy in reducing miscarriages	▪ 18.3 per cent have a miscarriage if TSH>2.5, anti-TPO ab positive if untreated ▪ 4.4 per cent have a miscarriage if TSH>2.5, anti-TPO ab positive and treated with thyroxine	Dosiou, 2012 citing Negro, 2006. Negro, 2007.

Note: anti-TPO=anti thyroid peroxidase antibody, TSH=thyroid stimulating hormone

Source: Abalovich, M. Gutierrez, S. Alcaraz, G. et al. 2002. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid, 12 (63). Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ 2000 Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 7:127–130. Casey BM, Dashe JS, Wells CE et al. Subclinical hypothyroidism and pregnancy outcomes. Obstetrics & Gynecology 2005; 105: 239–245.Dosiou, C. Barnes, J, Schwartz, A. et al. 2012. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. J Clin Endocrinol Metab. 97(5). Haddow JE, Palomaki GE et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. Journal of Medical Screening 2000; 7: 127–130. Lazarus, J. H. 2010. Thyroid function in pregnancy, British Medical Bulletin Advance Access, 1. Mitchell ML, Klein RZ, Sargent JD et al. Iodine sufficiency and measurements of thyroid function in maternal hypothyroidism. Clinical Endocrinology (Oxford) 2003; 58: 612–616. Negro, R. Formoso, G. Mangieri, T. Pezzarossa, A. Dazzi, D. and Hassan, H. 2006. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: Effects on obstetrical complications. The Journal of Clinical Endocrinology & Metabolism, 91(7). Negro, R. Schwartz, A. Gismondi, R. Tinelli, A. Mangieri, T. Stagnaro-Green, A. 2010. Universal screening vs. case finding for detection and treatment of thyroid dysfunction during pregnancy, J Clin Endocrinol Metabl, 95 (4). Negro, R. Mestman, J. H. 2011. Thyroid disease in pregnancy, Best practice & research clinical endocrinology & metabolism, 25(6). Stagnaro-Green, Abalovich, M. Alexander, E. et al. 2011. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum, Thyroid, 21(10). Vaidya B, Anthony S, Bilous M et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? Journal of Clinical Endocrinology and Metabolism 2007; 92: 203–207.

Cost of resource use

Table 4.5 lists the costs of screening and treatment of hypothyroidism. The costs of screening involve a TSH level test and anti-TPO test to determine an abnormal level TSH levels and if the woman is anti-TPO antibody positive. If the TSH result is within range the women will not undergoe further testing, this is the cost of a negative result for thyroid function screen.[17]

[17] Dosiou, C. Barnes, J, Schwartz, A. et al. 2012. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. J Clin Endocrinol Metab. 97(5).

If a women is hypothyroid (overt or subclinical), then an FT4 test is performed, this is followed by a 40 minute consultation with an endocrinologist to discuss results and treatment options. Therefore, the cost of a positive result includes the three tests and a consultation.

Treatment by thyroxine replacement therapy is given to women who have overt hypothyroidism and subclinical hypothyroidism with anti-TPO antibodies.

Thyroxine is usually given as 100mg daily tablets for the duration of pregnancy and postpartum for those with PPT. This amounts to 30 weeks pre-birth assuming the test is performed in week 10, with 6 months treatment postpartum. Additionally, women are required to have their TSH and FT4 levels retested every 6 weeks to titrate thyroxine dosage, meaning three TSH, FT4 and 10 minute endocrinologist consultations.

There is uncertainty regarding the cost of thyroxine as it is likely that some women may need higher or lower dosage depending on TSH levels and symptoms, thus 100mg of thyroxine may not be representative to the total population.

Testing costs were collected from MBS online and are based on 2013 dollars. The cost of thyroxine is the Dispensed Price for Maximum Quantity (DPMQ) listed on PBS. There is uncertainty regarding the true costs of testing and treatment as the PBS and MBS listed prices are not necessarily representative of the costs paid by hospitals, and do not include other hospital costs such as overheads.

The cost of an endocrinologist consultation is based on the average self-reported pre-tax income for medical specialists (adjusted for age, experience and hours worked) of $152 per hour, which would cover income plus costs associated with running a private practice.[18] For the purposes of simplicity, the cost of a 40 minutes (long) consultation is assumed to be equivalent to the cost of an hour of endocrinologist time.

4.5 Costs of screening and treatment for hypothyroidism

Item	Cost	Reference
TSH quantification	25.05	MBS, 66716, full fee
FT4 testing	34.8	MBS, 66719, full fee
Anti-TPO testing	34.55	MBS, 71165, full fee
Endocrinologist consultation (40 minutes)	20.13	Western Australia Department of Training and Workforce Development
Positive result for thyroid function screen	**114.53**	
TSH quantification	25.05	MBS, 66716, full fee
Anti-TPO testing	34.55	MBS, 71165, full fee

[18] This rate is higher than the published available estimates for endocrinologist salaries, which are in the order of $45 per hour and would not include practice running costs. The published rates for endocrinologists are also expected to relate only to young entrants to the profession and they are not used because they are not in line with the experience of costs understood to be faced by hospitals.

Item	Cost	Reference
Negative result for thyroid function screen	**59.6**	
Thyroxine treatment 100mg for pre-birth and 6 months postpartum	45.72	PBS, 2175L, DPMQ. Nicholson, 2006
TSH tests to titrate thyroxine treatment, 3 tests	75.15	
FT4 tests to titrate thyroxine treatment, 3 tests	104.4	
Endocrinologist consultation (10 minutes), 3 visits	22.65	
Treatment for overt hypothyroidism and subclinical hypothyroidism with anti-TPO antibody	**247.92**	

Note: Australian dollars, Prices were inflated to 2012 dollars. MBS and PBS costs were accessed in 2013.

Source: MBS Online and PBS Online, accessed 9 September 2013. Western Australia Department of Training and Workforce Development, accessed 18 September 2013 <http://www.careercentre.dtwd.wa.gov.au/occupations/Pages/endocrinologist.aspx?> Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR 2006 Prevalence of postpartum thyroid dysfunction: a quantitative review. Thyroid 16:573–582. Forehan S. Thyroid disease in the perinatal period. Aust Fam Physician. 2012 Aug;41(8):578-81.

Cost of potential consequences

The evidence surrounding thyroid dysfunction and adverse obstetrical and fetal outcomes is insufficient to pinpoint the specific outcomes to be measured from screening and treatment. That is, it is uncertain if, and to what extent, hypothyroidism during pregnancy affects the chances of preterm delivery, miscarriage or having PPT.[19]

The key consequences that are relevant to the assessment of alternative strategies for screening include:

- preterm delivery
- miscarriage, and
- postpartum thyroiditis.

The costs associated with these consequences will inevitably vary depending on maternal outcomes and outcomes for the newborn.

The cost of preterm delivery varies because of the range of circumstances that can affect cost outcomes. Compared to normal term delivery, in most cases there will be added costs of care for preterm babies with extended bed days. The average length of stay for disorders related to short gestation and low birth weight in public hospitals is 17.8 days and 13.5 days for private hospitals.[20]

The cost of later term miscarriage with respect to hospital care (bed days and staff) can be similar to that of a live birth, although again there is wide variation in cost outcomes. For instance, early stage miscarriages typically do not require admission and are treated

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19 Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. Cochrane Database Syst Rev. 2013 May 31;5.

20 Australian Institute of Health and Welfare, 2012, Australian hospital statistics 2010-11, Admitted patient care-Principal diagnoses (Part 2), AIHW.

expectantly. Later stage miscarriages may be managed as an outpatient or day surgery case if the mother requires a dilation and curettage.

There are also emotional and psychological burdens experienced by the woman and her family, which are difficult to quantify despite the impacts being real.

Further, there is a chance that women will experience PPT, which in itself is transitory in nature. This involves:

- a transient period of hyperthyroidism occurring between 1 to 3 months postpartum and lasting 2-8 weeks, and
- a transient period of hypothyroidism occurring between 4 to 6 months postpartum.[21]

The costs of PPT include the treatment of hypothyroidism with thyroxine replacement therapy with regular TSH level and FT4 level testing to determine thyroxine dosage. Hyperthyroidism is not usually treated as this state is transient and anti-thyroid drugs can be damaging, however, beta blockers (propranolol) can be used to treat symptoms.[22]

A proportion (1 in 5) of women will remain with persistent states of overt or subclinical hypothyroidism, in these cases the costs of long-term thyroxine replacement and monitoring must be considered.[23]

[21] Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR 2006 Prevalence of postpartum thyroid dysfunction: a quantitative review. Thyroid 16:573–582.

[22] Forehan S. Thyroid disease in the perinatal period. Aust Fam Physician. 2012 Aug,41(8):578-81.

[23] Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR 2006 Prevalence of postpartum thyroid dysfunction: a quantitative review. Thyroid 16:573–582.

5 Key findings and next steps

There is uncertainty surrounding key parameters that must be addressed before a complete economic evaluation can be performed.

In particular, the costs of (avoidable) adverse outcomes cannot be derived at this time due to the lack of robust evidence on the extent to which hypothyroidism during poregnancy affects the chances of preterm delivery or miscarriage, and any adverse obstetrical and neonatal outcomes.

The additional clinical evidence required for a complete economic evaluation includes adverse outcomes caused by subclinical hypothyroidism, the effectiveness of thyroxine replacement therapy in improving these outcomes, and the accuracy of the tests.

Hence there needs to be robust evidence that treatment works, and that any benefits can be attributed to the scan.

No relevant Australian economic evaluations were identified in the literature review.

Inadequate evidence base to support firm recommendations

Due to the lack of adequate RCTs showing the effectiveness of thyroxine replacement therapy in reducing adverse outcomes, modelling of the cost-effectiveness of thyroid function screening strategies cannot be properly performed given the current evidence and data.

There are limited existing economic evaluations, and studies evaluated were all American and one of them solely measuring the strategies against child IQ (Thung, 2009). Only one study included a risk-based screening comparator and based effectiveness of thyroxine replacement therapy on RCTs, however, there were limitations with this study.

Before screening strategies can be compared in an economic evaluation, the following data gaps must be filled:

- RCTs on hypothyroidism, both overt and subclinical and the associated adverse obstetrical or fetal outcomes
- RCTs on the effectiveness of thyroxine replacement therapy on the reduction on adverse outcomes
- the sensitivity and specificity of TSH, FT4 and anti-TPO tests in accurately identifying hypothyroid states, and
- expected compliance rates to thyroxine replacement therapy.

Once robust clinical evidence of the impacts of subclinical hypothyroidism and the effectiveness of treatment can be determined, a complete economic evaluation comparing either a risk-based or routine screening strategy could be performed.

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A Collection and appraisal of economic literature

Search strategy

A number of databases were searched for peer-reviewed literature on economic evaluations of the two prevention strategies for adverse obstetrical outcomes due to thyroid dysfunction in pregnant women. The search terms were developed in collaboration with the Department and included 'cost', 'pregnancy', 'hypothyroidism', 'thyroid' and 'screening' and 'thyroxine'.

The databases searched were Medline, CINAHL, Cochrane Library, Embase, EconLit and Science Direct.

Table A.1 lists the results of the searches.

A.1 Results of literature search strategy

Database	Terms	Results	Date
Medline	cost AND pregnancy AND (hypothyroidism OR thyroid)	81	8 August 2013
Cochrane Library	cost AND pregnancy AND (hypothyroidism OR thyroid)	3	8 August 2013
Embase	cost AND pregnancy AND (hypothyroidism OR thyroid)	28	8 August 2013
CINAHL	cost AND pregnancy AND (hypothyroidism OR thyroid)	11	8 August 2013
EconLit	cost AND pregnancy AND (hypothyroidism OR thyroid)	27	8 August 2013
Science Direct	cost AND pregnancy AND screening AND thyroid AND thyroxine	309	8 August 2013

Source: The CIE

The results of the searches were analysed by reviewing the abstracts and published full reports of studies that were identified as potentially relevant. These studies were assessed for inclusion in the literature review. The articles were assessed against a predetermined set of inclusion criteria.

Inclusion criteria and reasons for exclusion

The inclusion criteria are designed to assess whether the study is relevant to the issue being evaluated. Table A.2 illustrates the criteria developed for inclusion to be critically

appraised. The criteria is based on the format that The Cochrane Collaboration use for their systematic reviews of the literature.[24]

A.2 Inclusion and exclusion criteria for economic evaluations of strategies to prevent adverse obstetrical outcomes from thyroid dysfunction in pregnancy

Group	Inclusion criteria	Example reasons for exclusion
Types of studies	Economic evaluations	No relevant or useable data on cost or consequences
Participants	Pregnant women in the first trimester	Excludes pregnant population
Intervention	▪ Risk-based screening: – assessment of risk followed by screening and thyroxine treatment if applicable ▪ Routine screening: – screening of all women in first trimester and provision of thyroxine treatment if applicable ▪ No screening: – no screening	▪ Inappropriate intervention: – no interventions in the first trimester, only postpartum
Comparison	Risk-based screening vs. routine/universal screening vs. no screening	▪ Inappropriate comparator: – no inclusion of any relevant comparator
Outcome measures	ICER/QALY	No clinical outcomes are measured

Source: The CIE

The cost-effectiveness studies to be included for appraisal are listed in table A.3 along with studies that are excluded and reasoning for exclusion.

Very few economic evaluations were identified from the systematic literature review and these were restricted to studies performed in the U.S. After the initial assessment of the literature the inclusion criteria was broadened to allow appraisal of initially excluded articles. The only excluded article omitted the pregnant population from the study. The other included studies may not have all the relevant comparators (risk-based screening strategy) or compared screening at different times (postpartum).

[24] Higgins, J.P.T. Green, S. C. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (updated September 2006); In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

A.3 Economic evaluations to be included and reasons for exclusion

Title	Author	Year	Country	Note
Studies included for appraisal				**Outcome measure**
Universal and risk-based screening for autoimmune thyroid disease in pregnant women	Dosiou, C. Barnes, J. Schwartz, A. et al.	2012	United States of America	ICER/QALY, health outcomes included miscarriage, preterm labour, diagnosis of hypothyroidism and PPT
Universal screening in pregnancy for subclinical hypothyroidism	Thung, SF. Edmund, FF and Grobman, WA.	2009	United States of America	Marginal cost per QALY gained, child IQ
Screening pregnant women for autoimmune thyroid disease	Dosiou, C. Sanders, GD. Araki,SS. Crapo, LM.	2008	United States of America	ICER/QALY, health outcomes included gestational hypertension, PPT and low IQ
Universal prenatal and first trimester screening for postpartum thyroiditis	Bonds, DE. Freedberg, KA.	2001	United States of America	ICER/QALY gained, detection or prevention of PPT
Studies excluded from appraisal				**Reason for exclusion**
The 'abnormal' screening serum thyroxine (T4): Analysis of physician response, outcome, cost and health effectiveness	Epstein, KA. Schneiderman, LJ. Bush, JW. Zettner, A.	1981	United States of America	Patient group excluded pregnant population

Note: PPT: Postpartum thyroiditis

Source: The CIE

Critical appraisal

Once relevant studies had been identified for inclusion into the review, they were critically appraised for internal and external validity. The National Health and Medical Research Council (NHMRC) developed the appraisal items and grading system used.[25]

The critical appraisal is performed to determine if the study design and its findings are valid and if these results are generalisable or transferable to the Australian setting.

An assessment of internal validity addresses the issue of whether the results in the study are valid in its own setting. External validity or generalisability is a measure of whether the findings of the study are transferable to the current Australian health care system.

Value judgements are required in assessing internal and external validity and any points of contention were discussed and resolved with the Department.

[25] National Health and Medical Research Council, July 2001, How to compare the costs and benefits: evaluation of the economic evidence. Handbook series on preparing clinical practice guidelines, Canberra

Checklist for appraising economic evaluation studies

Table A.4 provides the checklist for critical appraisals, along with grading criteria and example reasons for a poor grading.

A.4 Critical appraisal framework for internal and external validity

Appraisal item or issue	Reason(s) for poor grading
Appraisal item for internal validity	**Y = item is clearly demonstrated, ? = some concern the item may not have been appropriately carried out, ?? = clear concerns about the item, NA = item is not applicable in the context**
Was the study question well defined?	Viewpoint for the evaluation is not clearly stated
Were appropriate health care options chosen and clearly described?	It is unclear who did what, to whom, where and how often for each health care option
Was an appropriate study type used?	Type of evaluation is unclear or incorrect
Was the effectiveness of the health care options established?	There is no evidence or there is weak evidence of the effectiveness of the health options and interventions
Were the cost estimates related to the baseline population risk?	Cost estimates are related to only a specific group, for instance, a high risk group
Were all the relevant costs and consequences identified for each health care option?	Relevant costs are not included in the evaluation
Were costs and consequences measured accurately?	▪ No allocation of shared resources such as hospital overheads ▪ Resource use not measured accurately
Were costs and consequences valued credibly?	▪ Pricing of resources is inaccurate, for instance, may be an inaccurate proxy. ▪ Prices are not adjusted for inflation
Was differential timing considered?	Future costs and consequences have not been discounted
Was incremental analysis performed?	No incremental analysis included
Was a sensitivity analysis performed?	No sensitivity analysis included
Were modelling techniques used in a clear and reasonable way?	Assumptions in the model are not clear or explicit
Appraisal issue for external validity	**A = study is generalisable to the proposed guideline setting with regard to this issue, B = some concerns relating to generalisability for this issue, C = study is not transferable to proposed guideline setting sufficient concern about this issue**
Patient group	The study focused on a different or specific population group with differing resource consumption
Health system setting	Health system setting is not comparable, in particular: ▪ older studies can include equipment no longer being in use ▪ health care institution differs in size or type of experience across personnel ▪ setting is not applicable to the rural and urban mix in Australia ▪ health care option cannot be transferred due to supply constraints in Australia

Appraisal item or issue	Reason(s) for poor grading
	▪ differences in incentive structures to health care professionals, institutions or patients
Health care option	Differences in: ▪ treatment options (types of medication or procedure) ▪ time spent as inpatient versus ambulatory care
Resource costs	▪ Resource costs have not been disaggregated enough so that prices in international studies can be adjusted to Australian dollars ▪ Resource consumption due to differing health care option leads to costs that cannot be transferred to the Australian setting
Marginal versus average cost	Inappropriate use of marginal or average costing depending on what is being evaluated
Other specific issues relating to the guideline	There may be specific issues or drivers that would prevent the transferability of a study to the current Australian context

Source: National Health and Medical Research Council, July 2001, How to compare the costs and benefits: evaluation of the economic evidence. Handbook series on preparing clinical practice guidelines, Canberra

Table A.5 shows the validity assessment of the cost effectiveness studies included for review.

A.5 Critical appraisal of economic evaluation of strategies to prevent adverse obstetrical outcomes due to thyroid dysfunction

Appraisal item or issue	Grade
Dosiou, C. et al. 2012	
Internal validity	
Was the study question well defined?	Y
Were appropriate health care options chosen and clearly described?	Y
Was an appropriate study type used?	Y
Was the effectiveness of the health care options established?	Y
Were the cost estimates related to the baseline population risk?	Y
Were all the relevant costs and consequences identified for each health care option?	Y
Were costs and consequences measured accurately?	Y
Were costs and consequences valued credibly?	Y
Was differential timing considered?	Y
Was incremental analysis performed?	Y
Was a sensitivity analysis performed?	Y
Were modelling techniques used in a clear and reasonable way?	Y
The cost-utility analysis compared strategies to detect autoimmune thyroid disease in pregnant women, the strategies included universal screening, screening of high-risk women and no screening. The costs include the laboratory tests (anti-TPO ab test, TSH test, TT4 test and FT4 test), treatment with levothyroxine, outpatient consultations and the workup of unscreened women. The consequences include preterm delivery, miscarriage, PPT, overt hypothyroidism over lifetime of mother and lower infant IQ. The measured outcome	

Appraisal item or issue	Grade
was cost per QALY gained. Findings were that risk-based screening and universal screening were cost-effective compared to no screening, with risk-based screening having a lower cost effective ratio.	
Internally valid?	**Yes**
External validity	
Patient group	A
Health system setting	C
Health care option	B
Resource costs	A
Marginal versus average cost	A
The patient group is pregnant women based in the American health care system. It is unlikely that care and resource use will be transferable to the Australian context. The effectiveness data was based on two RCTs in a small group in Italy which is known to be characterised by moderate iodine deficiency as iodised salt is not compulsory by law.[1] Price years are reported in 2009 US dollars, adjusting to current AUD is possible.	
Externally valid?	**No, sufficient concern over the transferability of the results.**
Thung, S. F. et al. 2009	
Internal validity	
Was the study question well defined?	Y
Were appropriate health care options chosen and clearly described?	Y
Was an appropriate study type used?	Y
Was the effectiveness of the health care options established?	?
Were the cost estimates related to the baseline population risk?	Y
Were all the relevant costs and consequences identified for each health care option?	Y
Were costs and consequences measured accurately?	Y
Were costs and consequences valued credibly?	?
Was differential timing considered?	?
Was incremental analysis performed?	Y
Was a sensitivity analysis performed?	Y
Were modelling techniques used in a clear and reasonable way?	Y
Cost-utility analysis to determine the costs and consequences of universal screening compared to no screening for thyroid function. Costs include screening (TSH test, FT4 tests, nurse consultation) and treatment (thyroxine replacement therapy and consultation with endocrinologist). Consequences include the cost of care and utility of low child IQ (IQ < 70 and IQ from 70-80). There was no RCT data on the effectiveness of levothyroxine therapy on the reduction of poor health outcomes such as low IQ. The valuation of utilities was unclear and discounting on consequences was not reported. The measured outcome is cost per QALY gained.	

Appraisal item or issue		Grade
Findings were that universal screening was the dominant strategy compared to no screening		
Internally valid?	**Issues with measurement and valuation of utilities and effectiveness of thyroxine replacement therapy on IQ levels.**	
External validity		
Patient group		A
Health system setting		C
Health care option		C
Resource costs		A
Marginal versus average cost		A
The patient group was pregnant women in the US health care system. It is unlikely that care and resource use will be transferable to the Australian context. The health care options did not include a strategy of risk-based screening which is the current recommendation in Australia. Prices are reported in 2007 US dollars. Adjusting to current AUD is possible.		
Externally valid?	**No, sufficient concern over the transferability of results.**	
Dosiou, C. et al. 2008		
Internal validity		
Was the study question well defined?		Y
Were appropriate health care options chosen and clearly described?		Y
Was an appropriate study type used?		Y
Was the effectiveness of the health care options established?		?
Were the cost estimates related to the baseline population risk?		Y
Were all the relevant costs and consequences identified for each health care option?		Y
Were costs and consequences measured accurately?		Y
Were costs and consequences valued credibly?		?
Was differential timing considered?		Y
Was incremental analysis performed?		Y
Was a sensitivity analysis performed?		Y
Were modelling techniques used in a clear and reasonable way?		Y
Cost-utility analysis on the screening of pregnant women for thyroid dysfunction, strategies were universal screening for either TSH or anti-TPO in the first trimester compared to no screening. The costs include the laboratory tests (anti-TPO test, TSH test, TT4 test and FT4 test), treatment with levothyroxine, outpatient consultations and the work-up of unscreened women. Consequences include utilities of women with subclinical hypothyroidism or overt hypothyroidism on PPT, gestational hypertension and a child with IQ<85. There was no RCT data on the effectiveness of levothyroxine therapy on the reduction of poor health outcomes such as low IQ. The valuation of utilities was unclear. Findings were that the universal screening for autoimmune thyroid dysfunction in the first trimester was cost-effective compared to no screening.		

Appraisal item or issue		Grade
Internally valid?	**Concern over the results due to lack of effectiveness data and on how utilities were valued.**	
External validity		
Patient group		A
Health system setting		C
Health care option		C
Resource costs		A
Marginal versus average cost		A
The patient group was pregnant women in the US health care system. It is unlikely that care and resource use will be transferable to the Australian context. The health care option did not include a risk-based screening strategy which is the current recommendation in Australia. Prices are reported in 2004 US dollars. Adjusting to current AUD is possible.		
Externally valid?	**No, sufficient concern over the transferability of results**	
Bonds, et al. 2001		
Internal validity		
Was the study question well defined?		Y
Were appropriate health care options chosen and clearly described?		Y
Was an appropriate study type used?		Y
Was the effectiveness of the health care options established?		?
Were the cost estimates related to the baseline population risk?		Y
Were all the relevant costs and consequences identified for each health care option?		?
Were costs and consequences measured accurately?		?
Were costs and consequences valued credibly?		?
Was differential timing considered?		NA
Was incremental analysis performed?		Y
Was a sensitivity analysis performed?		Y
Were modelling techniques used in a clear and reasonable way?		Y
Cost-utility analysis to analyse screening strategies for the detection of PPT (both hypothyroid and hyperthyroid states), the strategies include TPO test at first trimester, TSH test at 6 weeks postpartum and no screening. Some data on the effectiveness of the health care options were derived from the literature (no systematic literature review), others were assumptions by the author with no justification for the values given. Costs included screening (TPO test, TSH test, T4 tests, radioactive iodine tests) and treatment (physician visits, further thyroid function tests, propylthiouracil, thyroid replacement therapy and counselling/medication for depression). Consequences included utilities of women PPT, with or without Type 1 diabetes. Women with PPT with either no symptom, symptomatic and undiagnosed, symptomatic and diagnosed or symptomatic and incorrectly diagnosed as depressed. The source or method of measurement for the utilities was not provided.		

Appraisal item or issue	Grade
Found that the TSH strategy at 6 weeks postpartum was cost-effective compared to TPO testing at first trimester and no screening, in both the general pregnant population and particularly in women with diabetes. However, the sensitivity analysis revealed that the cost-effectiveness results were most sensitive to test characteristics such as sensitivity, specificity and costs (TPO antibody test and TSH tests).	
Internally valid?	**Concern over the results due to lack of effectiveness data and on how utilities were valued.**
External validity	
Patient group	A
Health system setting	C
Health care option	C
Resource costs	A
Marginal versus average cost	A
The patient group was pregnant women in the US health care system. It is unlikely that care and resource use will be transferable to the Australian context. The strategies are not transferable to the Australian context, if testing was to occur in first trimester for PPT, there would be thyroid function tests first (TSH testing, not TPO), this will be followed on by FT4 and anti-TPO testing. Further, in Australia women who are at high risk of thyroid dysfunction in pregnancy should be tested, Type 1 diabetes is one of these risks, there should have been an explicit strategy to test high-risk populations. Prices are reported in 1999 US dollars. Adjusting to current AUD is possible.	
Externally valid?	**No, sufficient concern over the transferability of results.**

Note: Internal validity grades include: Y = item is clearly demonstrated, ? = some concern the item may not have been appropriately carried out, ?? = clear concerns about the item, NA = item is not applicable in the context. External validity grades include: A = study is generalisable to the proposed guideline setting with regard to this issue, B = some concerns relating to generalisability for this issue, C = study is not transferable to proposed guideline setting sufficient concern about this issue. Appraisal guidelines from National Health and Medical Research Council, July 2001, How to compare the costs and benefits: evaluation of the economic evidence. Handbook series on preparing clinical practice guidelines, Canberra. Abbreviations: AUD(Australian dollars),FT4 (free thyroxine), IQ (intelligence quotient),PPT(postpartum thyroiditis), QALY (quality adjusted life years) and RCT (randomised controlled trial),TPO-Ab (thyroid peroxidase antibody), TSH (thyroid stimulating hormone), TT4 (Total thyroxine)

Source: The CIE. [1] Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. Cochrane Database Syst Rev. 2013 May 31;5

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