Subclinical hypothyroidism and hypothyroidism in pregnancy

Objectives: To provide advice on testing and treatment of hypothyroidism in pregnancy

Target audience: Health professionals providing maternity care, and patients.

Values: The evidence was reviewed by the Women’s Health Committee (RANZCOG), and applied to local factors relating to Australia and New Zealand.

Validation: This statement was compared with American Thyroid Association (ATA) and Endocrine Society and ACOG guidance on this topic.

Background: This statement was first developed by Women’s Health Committee in July 2012 and reviewed in July 2015 and in July 2018

Funding: The development and review of this statement was funded by RANZCOG.

First endorsed by RANZCOG: July 2012
Current: July 2018
Review due: July 2021

This statement has been developed and reviewed by the Women’s Health Committee and approved by the RANZCOG Board and Council.

A list of Women’s Health Committee Members can be found in Appendix A.

Disclosure statements have been received from all members of this committee.

Disclaimer: This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.
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1. **Patient summary**

The thyroid is a gland in the neck that produces thyroid hormone. This hormone controls how your body uses energy (your “metabolism”), and is essential for normal health. Thyroid hormone is particularly important in pregnancy because it is required for normal pregnancy and the development of the baby. A lack of thyroid hormone, or “hypothyroidism” is most commonly caused by autoimmune disease or iodine deficiency. An underactive thyroid may not cause any symptoms, or may cause very low energy levels, feeling cold easily, hair loss or constipation. If untreated, very low levels of thyroid hormone can lead to pregnancy complications and affect the intellectual development of the baby. The diagnosis is made with a blood test, and the treatment is supplementation with thyroid hormone tablets (“thyroxine”). Minor changes in thyroid function do not cause problems during the pregnancy, or for the baby after birth.

2. **Summary of recommendations**

<table>
<thead>
<tr>
<th>Recommendation 1</th>
<th>Grade</th>
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</table>
| Women who are pregnant, planning a pregnancy or breast feeding should take an iodine supplement of 150 micrograms (µg) each day. | Consensus-based recommendation
|

<table>
<thead>
<tr>
<th>Recommendation 2</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Targeted testing for overt hypothyroidism is recommended in pregnancy. Women with a personal history of thyroid disease or symptoms of thyroid disease should be tested with TSH and FT4</td>
<td>Consensus-based recommendation</td>
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<thead>
<tr>
<th>Recommendation 3</th>
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<tbody>
<tr>
<td>Overt hypothyroidism should be treated in pregnancy. Overt hypothyroidism is defined as a TSH above the reference range with a decreased T₄, OR TSH &gt;10 mIU/L, irrespective of the level of FT4.</td>
<td>Consensus-based recommendation</td>
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<tr>
<th>Recommendation 4</th>
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<tbody>
<tr>
<td>Screening for subclinical hypothyroidism or TPO antibodies, and subsequent treatment with thyroxine is not recommended in pregnancy</td>
<td>A</td>
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3
3. Introduction

3.1 Aetiology of hypothyroidism
The main cause of hypothyroidism in Australia and New Zealand is Hashimoto’s thyroiditis. Hashimoto’s is an autoimmune disorder and has an association with other autoimmune diseases such as Type 1 diabetes mellitus. Hypothyroidism can also be a result of: prior destruction of the thyroid gland (with radio-active iodine treatment); damage to the thyroid through radiation exposure; or, removal of the thyroid gland as a treatment for benign nodules, malignancy, or hyperthyroidism.

3.2 Physiology of thyroid hormone production in pregnancy
βHCG is structurally similar to TSH and provides weak thyroid stimulating activity, and so the normal increase in βHCG in early pregnancy may cause a small transient increase in free T4 (FT4) with subsequent TSH suppression.

The increased renal blood flow and glomerular filtration rate in pregnancy leads to increased iodine clearance and, therefore, the need for increased iodine intake during pregnancy. In women with pre-existing thyroid disease, the thyroid gland cannot respond to the physiological demands of pregnancy, and so increased thyroid replacement is required during pregnancy.

The fetus is reliant on transplacental transfer of maternal thyroid hormone until the fetal thyroid starts to become functional from 12 weeks. The fetus and the fully breastfed infant are dependent on maternal iodine for thyroid hormone synthesis.

The NHMRC recommends that all women who are pregnant, planning a pregnancy or breast feeding should take an iodine supplement of 150µg iodine daily. This is provided in many pregnancy multivitamin preparations.

### Recommendation 1

**Women who are pregnant, planning a pregnancy or breast feeding should take an iodine supplement of 150 micrograms (µg) each day.**

**Grade**

Consensus-based recommendation

3.2.1 Pregnancy specific ranges for thyroid function

**TSH**
Local pregnancy specific reference intervals should be used if available, but if these are not available, reference ranges can be defined as 0.5 mU/L less than the non-pregnant range in first trimester, and the same as the non-pregnant range in trimester 2 and 3, or, 4 mU/L can be used as the upper limit of the normal range throughout pregnancy.

**FT4**
FT4 concentrations also change with increasing gestation. As there is no single international method for standardisation of free thyroid hormone tests, method specific reference intervals are necessary for free thyroid hormone assays.
3.3 Diagnosis
Overt hypothyroidism is defined as increased serum TSH and decreased FT4, or, TSH >10mIU/L with FT4 within the normal range.

Subclinical hypothyroidism is defined as serum TSH above the reference range, and FT4 within the normal range.

4. Recommendations

4.1 Overt Hypothyroidism (OH)
Overt hypothyroidism is uncommon in pregnancy as it is associated with anovulation and increased rates of miscarriage. Overt hypothyroidism (OH) is also associated with adverse effects on pregnancy and fetal development, including increased risks of preeclampsia, placental abruption, anaemia and postpartum haemorrhage, prematurity and perinatal mortality. In addition, overt hypothyroidism during pregnancy has been linked to developmental delay in children. Adequately treated hypothyroidism is not associated with any adverse maternal, fetal or neonatal complications.

4.1.1 Testing for overt hypothyroidism in pregnancy
Maternal overt hypothyroidism is of similar prevalence to other conditions in which testing has been advocated, a reliable, acceptable test is available, and the beneficial effects of treatment of overt hypothyroidism have been well demonstrated. Thyroid function testing with serum TSH should be performed in early pregnancy for women with symptoms of thyroid disease or a personal history of thyroid disease.

<table>
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4.1.2 Treatment of overt hypothyroidism in pregnancy
Pregnant women receiving thyroxine for pre-existing thyroid disease will often require a 30-50% increase in their thyroxine dose form early in the first trimester (two extra doses/ week). Women with OH should have TSH levels performed at least once per trimester to assess the adequacy of their replacement therapy. The treatment goal for OH should be to maintain maternal serum TSH values within the lower half of trimester-specific pregnancy ranges.

<table>
<thead>
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<tr>
<td>Overt hypothyroidism should be treated in pregnancy. This includes women with a TSH above the reference range with a decreased T4, AND all women with a TSH &gt;10 mIU/L, irrespective of the level of FT4.</td>
<td>Consensus-based recommendation</td>
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4.2 Subclinical Hypothyroidism (SCH)

Subclinical hypothyroidism (SCH) in pregnancy is defined as a TSH level above the pregnancy-related reference range with a normal serum FT4 concentration.

4.2.1 Pregnancy outcomes with SCH

There have been numerous retrospective studies reporting associations between SCH and adverse pregnancy outcomes, however, the data is inconsistent, with many studies failing to demonstrate an adverse effect from untreated SCH. Results from large cohorts and meta-analyses have also not been consistent in demonstrating an association between SCH and adverse pregnancy outcomes \(^{8-11}\). High quality prospective randomized controlled trials involving over one hundred thousand women have not demonstrated any maternal or neonatal benefits from treatment of SCH with thyroxine \(^{12,13}\).

4.2.2 Neurological outcome and SCH

The documented association between overt hypothyroidism and childhood developmental delay has not been confirmed in prospective cohort data of women with SCH \(^{14-15}\). The two high quality randomised controlled intervention studies, described above, did not show improved cognitive function in children at 3 or 5 years of age after antenatal screening and maternal treatment for subclinical hypothyroidism \(^{12-13}\). Criticism has been raised of the validity of these trials because thyroxine treatment was not commenced until early second trimester.

4.2.3 Screening for subclinical hypothyroidism

Screening of pregnant women and the subsequent management of SCH and or thyroid autoantibodies has been a controversial issue. Some professional societies recommended widespread targeted screening \(^3\) however others do not \(^{16}\). A single study aimed at comparing treatment for SCH using a universal screening versus a case finding approach to SCH did not find a difference in overall outcome between the two groups \(^{17}\). Due to the absence of benefit of treatment of SCH in pregnancy, screening is not recommended.

4.3 Thyroid autoantibodies

Two small non-placebo controlled trials in euthyroid, TPO Ab-positive women appeared to show a benefit for reduction of preterm birth with thyroxine treatment, however this benefit has not been confirmed in two other studies \(^{18-21}\). There is no substantive evidence to support alteration in TSH targets or benefits from thyroxine treatment based on TPO antibody status and so universal or targeted screening for thyroid autoantibodies is not recommended in pregnancy.

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4.4 Miscarriage and thyroid function

An association exists between maternal SCH, or TPO antibodies, and miscarriage \(^{22}\). Trials of intervention to prevent miscarriage in women with SCH or TPO antibodies have generally been of low methodological quality and have had heterogeneous results \(^{18,20}\). The results of an ongoing, international, multi-centre, placebo controlled trial of thyroxine in euthyroid women with TPO
antibodies who are recruited and treated prior to pregnancy to reduce miscarriage are expected in 2018, and will better inform decisions around the role of thyroxine in prevention of miscarriage\textsuperscript{23}.

5. References

1. Iodine Supplementation for Pregnant and Breastfeeding Women, NHMRC Public Statement 2010
2. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum Authors: Erik K. Alexander, Elizabeth N. Pearce, Gregory A. Brent, et al
6. Tan, T. Cheng, Y. Caughey, A. Are women who are treated for hypothyroidism at risk for pregnancy complications? AJOG 194: 5 2006


21. Casey, B Thyroid peroxidase antibodies in women with subclinical hypothyroidism or hypothyroxinemia American Journal of Obstetrics & Gynecology, Volume 216, Issue 1, S47


6. Links to other College statements

(C-Gen 15) Evidence-based Medicine, Obstetrics and Gynaecology

7. Patient information

A range of RANZCOG Patient Information Pamphlets can be ordered via:

https://www.ranzcog.edu.au/Womens-Health/Patient-Information-Guides/Patient-Information-Pamphlets

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Appendices

Appendix A Women’s Health Committee Membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Position on Committee</th>
</tr>
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<tbody>
<tr>
<td>Professor Yee Leung</td>
<td>Chair</td>
</tr>
<tr>
<td>Dr Joseph Sgroi</td>
<td>Deputy Chair, Gynaecology</td>
</tr>
<tr>
<td>Associate Professor Lisa Hui</td>
<td>Member</td>
</tr>
<tr>
<td>Associate Professor Ian Pettigrew</td>
<td>EAC Representative</td>
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<tr>
<td>Dr Tal Jacobson</td>
<td>Member</td>
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<tr>
<td>Dr Ian Page</td>
<td>Member</td>
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<tr>
<td>Dr John Regan</td>
<td>Member</td>
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<tr>
<td>Dr Craig Skidmore</td>
<td>Member</td>
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<tr>
<td>Associate Professor Janet Vaughan</td>
<td>Member</td>
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<tr>
<td>Dr Bernadette White</td>
<td>Member</td>
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<tr>
<td>Dr Scott White</td>
<td>Member</td>
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<tr>
<td>Associate Professor Kirsten Black</td>
<td>Member</td>
</tr>
<tr>
<td>Dr Greg Fox</td>
<td>College Medical Officer</td>
</tr>
<tr>
<td>Dr Marilyn Clarke</td>
<td>Chair of the ATSI WHC</td>
</tr>
<tr>
<td>Dr Martin Byrne</td>
<td>GPOAC Representative</td>
</tr>
<tr>
<td>Ms Catherine Whitby</td>
<td>Community Representative</td>
</tr>
<tr>
<td>Ms Sherryn Elworthy</td>
<td>Midwifery Representative</td>
</tr>
<tr>
<td>Dr Amelia Ryan</td>
<td>Trainee Representative</td>
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Appendix B Contributing Authors

The Women’s Health Committee acknowledges the contribution from Dr Alexis Shub.

Appendix C Overview of the development and review process for this statement

i. Steps in developing and updating this statement

This statement was originally developed in July 2012 and was most recently reviewed in March 2018. The Women’s Health Committee carried out the following steps in reviewing this statement:

- Declarations of interest were sought from all members prior to reviewing this statement.
- Structured clinical questions were developed and agreed upon.
- An updated literature search to answer the clinical questions was undertaken.
- At the March 2018 face-to-face committee meeting, the existing consensus-based recommendations were reviewed and updated (where appropriate) based on the available body of evidence and clinical expertise. Recommendations were graded as set out below in Appendix B part iii)
Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of the Women’s Health Committee.

A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. The Women’s Health Committee members were required to declare their relevant interests in writing on this form prior to participating in the review of this statement.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this statement.

Grading of recommendations

Each recommendation in this College statement is given an overall grade as per the table below, based on the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades of Recommendations for Developers of Guidelines. Where no robust evidence was available but there was sufficient consensus within the Women’s Health Committee, consensus-based recommendations were developed or existing ones updated and are identifiable as such. Consensus-based recommendations were agreed to by the entire committee. Good Practice Notes are highlighted throughout and provide practical guidance to facilitate implementation. These were also developed through consensus of the entire committee.

<table>
<thead>
<tr>
<th>Recommendation category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence-based</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation(s) but care should be taken in its application</td>
</tr>
<tr>
<td>D</td>
<td>The body of evidence is weak and the recommendation must be applied with caution</td>
</tr>
<tr>
<td>Consensus-based</td>
<td>Recommendation based on clinical opinion and expertise as insufficient evidence available</td>
</tr>
<tr>
<td>Good Practice Note</td>
<td>Practical advice and information based on clinical opinion and expertise</td>
</tr>
</tbody>
</table>
Appendix C Full Disclaimer
This information is intended to provide general advice to practitioners, and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient.

This information has been prepared having regard to general circumstances. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual patient and the particular circumstances of each case.

This information has been prepared having regard to the information available at the time of its preparation, and each practitioner should have regard to relevant information, research or material which may have been published or become available subsequently.

Whilst the College endeavours to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available.