The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Testing for hypothyroidism during pregnancy with serum TSH

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.

First endorsed by RANZCOG: July 2012
Current: July 2015
Review due: July 2018

Objectives: To provide advice on the testing for hypothyroidism during pregnancy with serum TSH.

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.

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

Table of contents

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, low levels of thyroid hormone can lead to pregnancy complications and affect the intellectual development of the baby. The diagnosis can be performed with a blood test, and the treatment is supplementation with thyroid hormone tablets ("thyroxine").

2. Summary of recommendations

Recommendation 1	Grade
Overt hypothyroidism should be treated in pregnancy. This includes women with a TSH above the reference range with a decreased T_4, AND all women with a TSH >10 mIU/L, irrespective of the level of fT_4.	Consensus-based recommendation
Recommendation 2	**Grade**
Targeted testing for overt hypothyroidism is recommended in pregnancy.	Consensus-based recommendation
Recommendation 3	**Grade**
There is insufficient evidence to support universal TSH screening and treatment of subclinical hypothyroidism in pregnancy.	Consensus-based recommendation

3. Introduction

Thyroid disorders are common in pregnancy. The prevalence of overt hypothyroidism (OH) is estimated to be between 0.3% and 0.5% and the presence of subclinical hypothyroidism (SCH) around 2 to 3%.[1] Normal thyroid function is important during pregnancy for both maternal and fetal outcomes.

3.1 Aetiology of hypothyroidism

The main cause of hypothyroidism, worldwide, is iodine deficiency. However in areas that are iodine sufficient the main cause is Hashimoto's thyroiditis. Hashimoto's is an autoimmune disorder where the immune system makes antibodies against thyroglobulin (anti-TG) and/ or thyroid peroxidase (anti-TPO). There is an association with thyroid autoantibody positivity and 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

hCG is structurally similar to TSH and provides weak thyroid stimulating activity. The normal increase in hCG in early pregnancy may cause a small transient increase in FT_4 with subsequent TSH suppression towards the end of the first trimester.

During pregnancy, there is increased T_4 production and requirement due to: increased iodine uptake and thyroid hormone synthesis by the thyroid gland; increased hepatic production of thyroxine binding globulin (TBG) reducing the amount of biologically active T_4; increased volume of distribution of T_4 due to plasma volume expansion; and, transplacental passage of T_4 to the fetus. The fetus is solely reliant on transplacental transfer of maternal thyroid hormone for the first half of pregnancy with the fetal thyroid starting to become functional from 18 weeks. In the presence of pre-existing thyroid dysfunction, the thyroid gland cannot respond to the physiological demands of pregnancy, hence the need for increased thyroid replacement during pregnancy.

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. The fetus and the fully breastfed infant are entirely dependent on maternal iodine for thyroid hormone synthesis. The NHMRC recommends that all women who are pregnant, planning a pregnancy or breast feeding should receive 150μg iodine daily. This is provided in many pregnancy multivitamin preparations.

3.2.1 Trimester specific reference intervals for thyroid function

The alterations in thyroid function during pregnancy can pose challenges in interpretation of laboratory thyroid tests. In Australia currently, routine thyroid function tests assays measure free T_4 and free T_3. Total T_4 and total T_3 measurements are not widely available.

TSH

The decrease in serum thyroid stimulating hormone (TSH) during the first trimester has been well described.[2] Pregnancy specific reference intervals from the individual laboratory should be used if available, but the following table gives some guidance on appropriate gestational age reference ranges.

First trimester	0.1 to 2.5 (mIU/L)
Second trimester	0.2 to 3.0
Third trimester	0.3 to 3.0

Serum free thyroxine (fT4)

Serum free thyroxine (fT_4) 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.[2]

Interpretation of thyroid function results in pregnancy:

	TSH	free T_4
Normal function in pregnancy	Varies with gestation	Normal fT_4
Overt hypothyroidism	Increased TSH	Decreased fT_4
Subclinical hypothyroidism	Increased TSH	Normal fT_4

3.3 Diagnosis

Overt hypothyroidism is diagnosed by a serum thyroid stimulating hormone (TSH) elevation and decreased free T_4 (fT_4). Auto antibodies should be tested as part of the investigations to confirm the aetiology.

Subclinical hypothyroidism is diagnosed by serum TSH above the reference range, but a fT_4 within the normal range. Thyroid auto-antibodies occur in 50-60% of women with subclinical hypothyroidism in iodine sufficient areas.

4. Discussion and 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 associated with many adverse effects on pregnancy and fetal development, including increased risks of miscarriage, pregnancy induced hypertension, preeclampsia, placental abruption, anaemia and postpartum haemorrhage.[3] As well as these obstetric complications, there are increased risks of adverse outcomes for the offspring, including prematurity, low birth weight, and perinatal mortality. In addition, overt hypothyroidism during pregnancy has been linked to cognitive impairment and developmental delay in children (cretinism).

Adequately treated hypothyroidism is not associated with any adverse maternal, fetal or neonatal complications.[4] 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).[2] Women with OH should have TSH levels performed at least once per trimester to assess the adequacy of their replacement therapy.

Recommendation 1	Grade
Overt hypothyroidism should be treated in pregnancy. This includes women with a TSH above the reference range with a decreased T_4, AND all women with a TSH >10 mIU/L, irrespective of the level of fT_4.	Consensus-based recommendation

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 thyroxine 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 some studies failing to demonstrate an adverse effect from untreated SCH. Reported associations have included increased risks of placental abruption and preterm birth [5], early pregnancy loss[6], preeclampsia[7] and gestational diabetes[8]. However in a large prospective study with a total of 10,990 patients, maternal SCH was not associated with a consistent pattern of adverse pregnancy outcomes such as preterm labour, preterm delivery, miscarriage, or premature rupture of membranes.[9]

There is no conclusive evidence to support universal screening for SCH to improve obstetric outcomes. A 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.[10] A single study of euthyroid, thyroid Ab-positive women appeared to show a benefit for reduction of miscarriage and preterm birth with thyroxine

treatment, but this benefit has not been confirmed in other studies.[10]

4.2.2 Neurological outcome and SCH

Although an association between SCH and developmental delay in the offspring has been reported in observational data,[11] newer RCT evidence has shown no paediatric benefit of maternal treatment during pregnancy. The only available randomised controlled interventional study, which included 21,846 women, showed that antenatal screening and maternal treatment for subclinical hypothyroidism did not result in improved cognitive function in children at 3 years of age.[12]

4.3 Screening for hypothyroidism in pregnancy

4.3.1 Targeted testing for overt hypothyroidism in pregnancy

Maternal overt hypothyroidism is of similar prevalence to other conditions in which screening 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. Other authorities suggest screening in a wider group including age >30 years, from an area of known moderate to severe iodine insufficiency, or have a family history of thyroid disease, anti-TPO antibodies, type 1 diabetes, history of preterm delivery or miscarriage, history of head or neck radiation, morbid obesity (BMI ≥40 kg/m^2), or infertility.[2]

The treatment goal for OH should be to normalise maternal serum TSH values within trimester-specific pregnancy ranges (as a guide; first trimester: 0.1-2.5 mIU/L; second trimester: 0.2-3.0 mIU/L; third trimester 0.3-3.0 mIU/L).

4.3.2 Universal screening for subclinical hypothyroidism

Universal screening of pregnant women and the subsequent management of SCH +/- thyroid autoantibodies has been a controversial issue. Some professional societies have previously recommended universal or widespread targeted screening.[13] However, since the results of the Controlled Antenatal Thyroid Screening Study were published in 2012, which showed no benefit in cognitive function in the children of treated women [12], more recent guidelines from ACOG have not supported universal screening and treatment.[14] Similarly, universal screening for thyroid autoantibodies is not recommended in pregnancy.

4.4 Management recommendations

Recommendation 2	Grade
Targeted screening for overt hypothyroidism is recommended in pregnancy.	Consensus-based recommendation
Recommendation 3	**Grade**
There is insufficient evidence to support universal TSH screening and treatment of SCH in pregnancy.	Consensus-based recommendation

5. References

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11. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child, N Engl J Med. 1999;341(8):549-55.
12. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function, N Engl J Med. 2012;366(6):493-501.
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14. American College of Obstetricans and Gynecologists. Practice Bulletin No. 148: Thyroid Disease in Pregnancy, Obstetrics & Gynecology. 2015;125(4):996-1005.

6. Links to other College statements

(C-Gen 15) Evidence-based Medicine, Obstetrics and Gynaecology
http://www.ranzcog.edu.au/component/docman/doc_download/894-c-gen-15-evidence-based-medicine-obstetrics-and-gynaecology.html?Itemid=341

7. Patient information

A range of RANZCOG Patient Information Pamphlets can be ordered via:
http://www.ranzcog.edu.au/publication/womens-health-publications/patient-information pamphlets.html

Appendices

Appendix A Women's Health Committee Membership

Name	Position on Committee
Associate Professor Stephen Robson	Chair and Board Member
Dr James Harvey	Deputy Chair and Councillor
Associate Professor Anusch Yazdani	Member and Councillor
Associate Professor Ian Pettigrew	Member and Councillor
Dr Ian Page	Member and Councillor
Professor Yee Leung	Member of EAC Committee
Professor Sue Walker	General Member
Dr Lisa Hui	General Member
Dr Joseph Sgroi	General Member
Dr Marilyn Clarke	General Member
Dr Donald Clark	General Member
Associate Professor Janet Vaughan	General Member
Dr Benjamin Bopp	General Member
Associate Professor Kirsten Black	General Member
Dr Jacqueline Boyle	Chair of the ATSIWHC
Dr Martin Byrne	GPOAC representative
Ms Catherine Whitby	Community representative
Ms Sherryn Elworthy	Midwifery representative
Dr Nicola Denton	Trainee representative

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 July 2015. 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 July 2015 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)

ii. 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.

iii. 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.

Recommendation category		Description
Evidence-based	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
	D	The body of evidence is weak and the recommendation must be applied with caution
Consensus-based		Recommendation based on clinical opinion and expertise as insufficient evidence available
Good Practice Note		Practical advice and information based on clinical opinion and expertise

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.