LOCAL OPERATING PROCEDURE

CLINICAL POLICIES, PROCEDURES & GUIDELINES

Approved by RHW Safety and Quality Committee
December 2022

THYROID DISEASE IN PREGNANCY

This CBR is developed to guide clinical practice at the Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this CBR.

1. AIM

- Appropriate management of a woman with subclinical or overt thyroid disease in pregnancy

2. PATIENT

- Woman with known or suspected thyroid disease in pregnancy

3. STAFF

- Medical and midwifery staff

4. EQUIPMENT

- Nil

5. CLINICAL PRACTICE

Screening for Thyroid Disorders in Pregnancy

- Do not perform universal thyroid screening in pregnancy
- Recommend screening for any woman with the following risk factors:
  - History of past thyroid disease
  - Known thyroid antibody positivity
  - Age > 30 years
  - BMI >40
  - Personal or family history of autoimmune disease e.g. T1 diabetes mellitus, coeliac disease
  - Presence of goitre
  - Residing in an area of known iodine insufficiency
  - Use of medications that can affect thyroid function e.g. lithium, amiodarone
  - Past history of infertility, pregnancy loss or neck irradiation
- Ensure woman has adequate iodine intake in pregnancy (250 mcg/day) from diet and supplementation (most supplements contain 150mcg iodine). Do not measure urinary iodine as it only reflects recent (6-8 hours) iodine intake[12]
- Review any recent Thyroid Function Test (TFTs) results. Use trimester specific ranges (after 7 weeks amenorrhoea[15]) for each pathology laboratory. If no laboratory trimester specific ranges available, for Thyroid Stimulating Hormone (TSH) use an upper limit of 4.0 mU/l
  - Between 1-7 weeks amenorrhoea, use non-pregnant ranges[15]
- Refer to appendix 1 for management of abnormal TFTs
- Refer woman with current or past history of hyperthyroidism (even if they are now euthyroid/hypothyroid post treatment) to obstetric medicine clinic (or usual private endocrinologist if familiar with thyroid disease in pregnancy)
- Ensure the following test results available:
  - TFTs –TSH, free thyroxine (fT4), free triiodothyronine (fT3)
  - Thyroid Receptor Antibody (TRAb) or Thyroid Stimulating Immunoglobulin (TSI)
  - Thyroid Peroxidase Antibody (TPOAb)
- Follow documented management plan from obstetric medicine clinic/private endocrinologist

Management during Pregnancy

Subclinical Hypothyroidism

TSH > 4mU/L (regardless of fT4 and fT3 levels):

- Check anti-TPO and anti-thyroglobulin (TG) levels
- Commence thyroxine as per appendix 1
- Check fT4 and TSH every trimester. If TFTs are normal at 28-30 weeks, no further testing is required
- Recommend replacement with levothyroxine rather than liothyronine or desiccated thyroid extract preparations[2] in pregnancy
- Target TSH within the lower half of pregnancy specific ranges (0.1 - 2.5mU/L)
- Refer to obstetric medicine clinic if TSH > 4mU/L, there is difficulty targeting TSH to range, or if woman or general practitioner (GP) prefer

Overt Hypothyroidism

Known pre-existing hypothyroidism, or newly elevated TSH with low fT4 or fT3:

- Check anti-TPO and anti-TG levels
- Assess woman clinically for signs or symptoms of hypothyroidism e.g. very low energy levels, easily feeling cold, constipation, hair loss (awareness of the significant overlap with normal pregnancy symptoms, especially in the first 16 weeks)
- Increase thyroxine dose by 30% at conception if taking oral thyroxine prior to pregnancy
- Recommend replacement with levothyroxine rather than liothyronine or desiccated thyroid extract preparations[2] in pregnancy
- Refer to the obstetric medicine clinic for assessment and management (or a private endocrinologist if familiar with thyroid disease in pregnancy)
- Check fT4 and TSH every 4-6 weeks from commencement or increase in dose of treatment
- Repeat TFTs 4 weeks after any adjustment to thyroxine dose. If TFTs are normal at 28-30 weeks, no further testing is required
- Target TSH guided by the trimester specific normal ranges (from the specific pathology laboratory where the bloods were collected)

Hyperthyroidism

- Refer to the obstetric medicine clinic for assessment and management (or usual private endocrinologist if familiar with thyroid disease in pregnancy)
- Treat with antithyroid drugs if required (Propylthiouracil (PTU) is the preferred agent in the first trimester although carbimazole may be substituted after 10-12 weeks' gestation). Titrate to maintain fT4 and fT3 in the trimester specific normal range (from the specific pathology laboratory where bloods were collected)
- Monitor TFTs 4-8 weekly depending on the clinical status
- Measure TRAb every trimester in woman with thyrotoxicosis or history of Graves' disease
- Check fetal heart rate and document at each visit for TRAb positive women, and refer to department of MFM if there is sustained fetal tachycardia (>160bpm)
- Refer TRAb positive woman and woman with active graves hyperthyroidism for serial fetal ultrasounds at 28, 32 and 36 weeks gestation in department of medical imaging for assessment of fetal complications such as fetal growth restriction, fetal tachycardia (fetal goitre) and hydrops
- Refer women with suspected fetal hyperthyroidism or goitre to Maternal Fetal Medicine (MFM) or where there are very high levels of TRAb (>3 times the upper limit of normal)

Neonatal considerations[16]

- Consult with the neonatal team if TRAb is still elevated prior to birth or not known at birth (due to the risk of neonatal thyrotoxicosis)
    - If TRAB levels are negative, no specific neonatal follow-up is necessary
- Send cord blood for levels of TSH receptor antibodies if woman is TRAb positive or not known, so that newborns with negative antibodies can be discharged from follow-up (measurement of cord TSH and fT4 levels is not indicated)
    - Perform fT4 and TSH levels at day 3 to 5 , repeat at day 10 to 14 of life and follow clinically until 2 to 3 months
- Arrange pediatric follow up on discharge

Management in the immediate postpartum period

Subclinical or overt hypothyroidism

- On thyroxine prior to pregnancy
  - Reduce thyroxine dose back to non-pregnant dose immediately after birth,
  - Recheck TFTs after 4-6 weeks
- Not on thyroxine prior to pregnancy
  - Cease thyroxine if pregnancy dose <100 mcg/day
  - Reduce dose of thyroxine by 50% if pregnancy thyroxine dose ≥ 100 mcg/day
  - Recheck TFTs in 4-6 weeks
  - Aim to withdraw thyroxine, especially in woman who are TPOAb negative

TPOAb positive

- Observe TPOAb positive woman clinically for symptoms of thyroid disease
  - The woman is at significant risk (50-60%) of manifesting either transient hyperthyroidism followed by hypothyroidism, or worsening hypothyroidism[13]
  - In a woman with previous postpartum thyroiditis, the risk of recurrence is 70%[13]
- Check TFTs at 4 and 12 weeks' postpartum, or if symptoms develop

Hyperthyroidism

- Anticipate a flare in Graves' disease
- Continue antithyroid medication
- Check TFTs at 4 weeks' postpartum

6. DOCUMENTATION

- Medical Record
- Antenatal Card

7. EDUCATIONAL NOTES

- Thyroid dysfunction affects 2-3% of pregnant women[5]
- The national Health Measures Survey[24] found that overall women aged 16-44 years had sufficient iodine levels (median urinary iodine concentration (UIC) 121.0µg/L). It found that 18.3% had levels less than 50µg/L, and likewise 62.2% had UIC less than 150µg/L which is the recommended level by the World Health Organisation for pregnant and breastfeeding women [24]
- TSH falls in the first trimester, increasing towards non-pregnant levels in the second and third trimesters. Measuring TSH prior to 7 weeks will tend to overestimate the incidence of SCH[1,2]
- SCH is defined as elevated TSH and normal fT4 and fT3 as per trimester specific ranges. This affects up to 2.5% of pregnant women. Of these 85% will be thyroid antibody positive. SCH should be considered an indicator of potential risk for later development of overt hypothyroidism. The impact on pregnancy outcomes is uncertain and therefore treatment of this group is controversial. Treatment with thyroxine may reduce miscarriage and preterm birth[2], however, more recent randomized controlled trials showed no difference in miscarriage rates [17,18,19]
- There is some evidence that treating a TSH > 4 might reduce preterm delivery [20] but also some suggestion that over replacement should be avoided as elevated fT4 is associated with low birth weight in observational studies [21], and in a retrospective cohort study, treatment was associated with reduced miscarriage but higher preterm delivery, GDM and preeclampsia [22]
- Overt hypothyroidism is defined as a raised TSH and reduced fT4 and fT3 as per trimester specific normal ranges, prior to thyroxine therapy. This is associated with adverse effects on pregnancy and fetal development, including increased risk of preeclampsia, placenta abruption, anaemia and postpartum haemorrhage, prematurity and perinatal mortality[1]. Thyroxine treatment should be commenced immediately in this condition. Pregnant women will often require a 30-50% increase in their thyroxine in the first trimester[1,4]
- Thyroid antibody positivity i.e. thyroid peroxidase (TPO) or thyroglobulin (TG) antibodies is an asymptomatic condition which is associated with an increased risk of thyroid dysfunction in the future. These women may be at increased risk of subfertility and miscarriage. However, treatment with thyroxine has not been shown to reduce the risk of miscarriage. Similarly, in women undergoing fertility treatment, thyroxine does not improve pregnancy rates[1,2]
- In women with hyperemesis gravidarum who also have suppressed TSH levels, treatment of hyperthyroidism should not be undertaken without evidence of intrinsic thyroid disease (including goitre and/or thyroid autoantibodies). These women should be referred to the

Obstetric Medicine Clinic or a private endocrinologist familiar with thyroid disease in pregnancy[2]

- Subclinical hyperthyroidism is defined as a suppressed TSH but normal fT4 and tT3 as per trimester specific normal ranges[2]
- Isolated maternal hypothyroxinemia is diagnosed when only the fT4 is low with a normal TSH. Treatment of this condition is not recommended[2]
- Overt hyperthyroidism is defined as a suppressed TSH and elevated fT4 and fT3 as per trimester specific normal ranges. Uncontrolled maternal hyperthyroidism has been associated with fetal tachycardia, small for gestational age babies, prematurity, stillbirths and possibly congenital malformation[2]
- Graves' disease is an autoimmune disorder caused by the production of TRAbs that stimulate the thyroid gland. These antibodies do cross the placenta and can interact with the fetal thyroid. Although uncommon (2-5% of cases of Graves' disease in pregnancy), high or increasing levels of maternal TRAbs have been known to cause fetal or neonatal hyperthyroidism[2,4]
- It is difficult to find what constitutes 'high' levels of TRAbs, but general expert consensus opinion considers 'high' as $\geq$2-3 x upper limit of laboratory specific normal. The fetus or infant is more likely to have Graves' hyperthyroidism when the maternal TRAb value is more than three to five times the upper limit of normal. If TRAb levels are over three times the upper limit of normal, increased monitoring is necessary[16, 23]
- In the woman with Graves' disease requiring antithyroid drug therapy, fetal hyperthyroidism due to the woman's TRAbs is rare, since the antithyroid drugs also cross the placenta. Of potentially more concern to the fetus/neonate is the woman with prior treatment for Graves' disease (for example radioactive iodine or surgery) who no longer requires antithyroid drugs[16]
- Postpartum thyroiditis most commonly presents with isolated hypothyroidism, but a biphasic presentation, and isolated hyperthyroidism can occur: a high index of suspicion is warranted for diagnosis[2,4]

8. RELATED POLICIES PROCEDURES CLINICAL PRACTICE LOP

- Australian College of Midwives (ACM) Guidelines for consultation and referral
- Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy – Management
- Nausea and Vomiting in Pregnancy & Hyperemesis Gravidarum NSW Health GL2022_009

9. RISK RATING

- High

10. NATIONAL STANDARD

- Standard 5 - Comprehensive Care
- Standard 4 – Communicating for Safety
- Standard 2 – Partnering with Consumers

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REVISION & APPROVAL HISTORY

Endorsed RHW Safety and Quality Committee 15.12.22
Reviewed and endorsed Maternity Service CBR group 28/11/2022
Reviewed and endorsed Maternity Services LOPs group 25/10/16
Approved Quality & Patient Safety Committee 21/11/13
Endorsed Obstetrics LOPs 5/11/13

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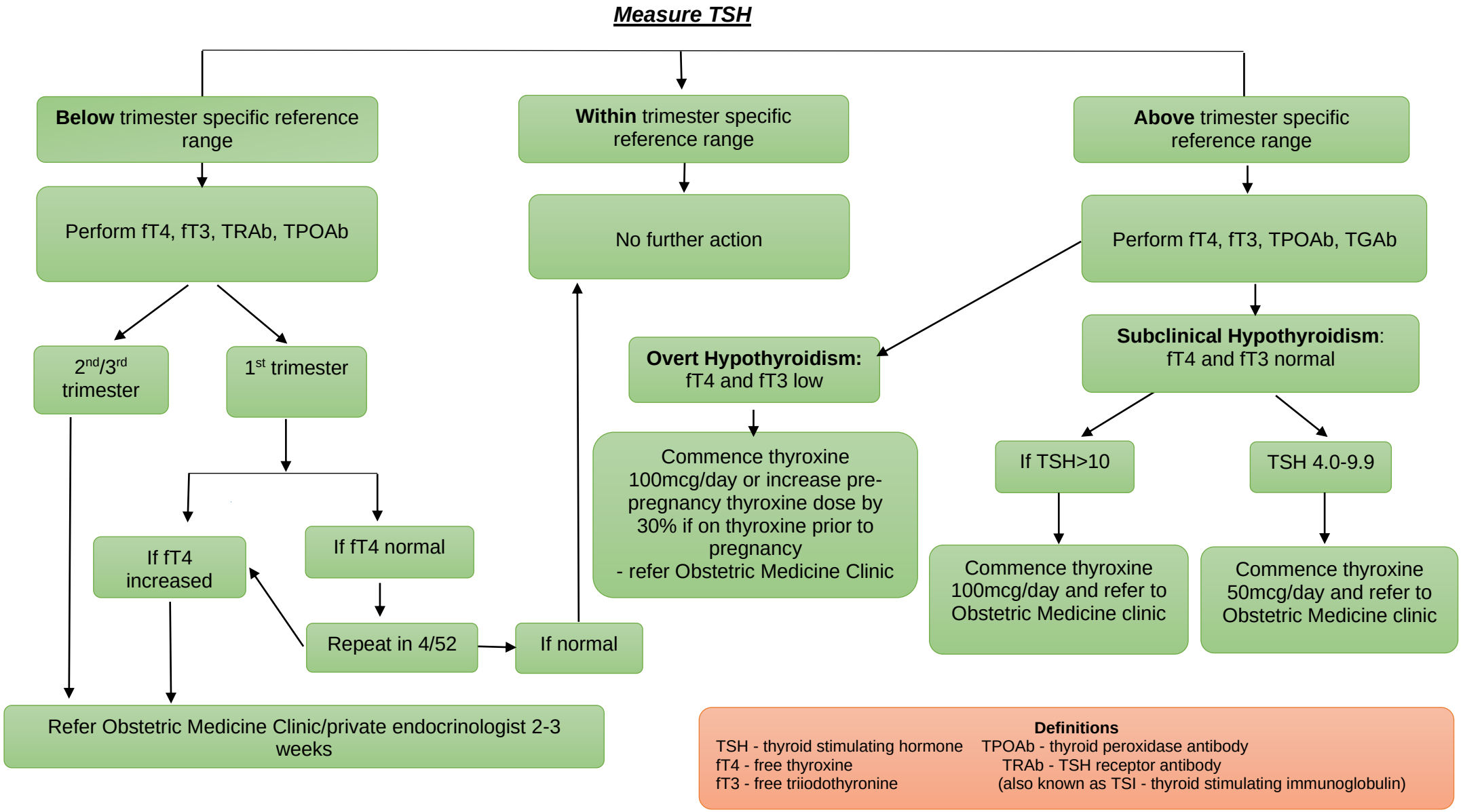
Appendix 1



Definitions

TSH - thyroid stimulating hormone
fT4 - free thyroxine
fT3 - free triiodothyronine
TPOAb - thyroid peroxidase antibody
TRAb - TSH receptor antibody
(also known as TSI - thyroid stimulating immunoglobulin)