Lothian Guidance for Diagnosis and Management of Thyroid Dysfunction in Pregnancy

Early diagnosis and good management of maternal thyroid dysfunction are essential to ensure minimal adverse effects on fetal development and maternal health. The following are suggestions for the use of thyroid function tests in Primary Care and are derived from the UK guidelines, modified to take into account local practice.

Diagnosis and Management of Thyroid Disease in Pregnancy

This requires close liaison between the GP, Community Midwife, Endocrinologist and Obstetrician. Much of the thyroid function testing is likely to be undertaken by the Community Midwives. However, the initial set of thyroid function tests requested for screening purposes or to check thyroid status in patients with established thyroid disorders is more likely to be done by the GP.

General Points

Maternal FreeT4 (FT4) and Free T3 (FT3) rather than total hormone concentrations must be measured in pregnancy. This is because Total T4 and Total T3 increase in pregnancy due to increased serum concentrations of thyroid hormone binding proteins. It is only the FT3 and FT4 fraction (not the bound fraction) that can enter cells and modify metabolism. Trimester-specific reference ranges for FT3 and FT4 need to be applied for diagnosis as their concentrations fall during pregnancy (see below).

<table>
<thead>
<tr>
<th></th>
<th>First trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4 pmol/L</td>
<td>10–18</td>
<td>9-16</td>
<td>8-14</td>
</tr>
<tr>
<td>FT3 pmol/L</td>
<td>3.4–6.6</td>
<td>3.2– 6.2</td>
<td>3.2-5.6</td>
</tr>
<tr>
<td>TSH mU/L</td>
<td>≤0.01 –3.4</td>
<td>0.06 – 3.4</td>
<td>0.17 – 3.4</td>
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Screening for thyroid disorders in pregnancy

The following categories of patient should be screened for thyroid disease using TSH and FT4 preferably prior to conception or if not at booking:

- Type 1 and Type 2 diabetes
- Other autoimmune disorders e.g. coeliac disease etc
- Previous history of thyroid disease
- Current thyroid disease
- Family history of thyroid disease (1st degree relative)
- Goitre or other features of thyroid disease

Hypothyroidism and Pregnancy

Overt untreated hypothyroidism is associated with foetal loss, poor perinatal outcome and severe neurodevelopmental delay. The developing foetal brain requires optimal thyroxine levels from early in the first trimester of pregnancy, before foetal production of thyroid hormones begins at 12 weeks gestation. Therefore in pregnancy there is an increased requirement for T4 [1,2,3]. The offspring of women whose free thyroxine levels are in the lowest 10% of the reference range in the first trimester of pregnancy have been shown to be at risk of significant neurodevelopmental delay at the age of two years [4].

The increase in serum free thyroxine (FT4) levels in women early in normal pregnancy does not occur in women who are hypothyroid. It is thus very important to ensure adequate thyroxine replacement from as early as 5 weeks gestation [5]. It is recommended that patients with established hypothyroidism should have the T4 dose increased by 25 micrograms when a pregnancy is confirmed. The recommended treatment of maternal hypothyroidism is administration of oral LT4. Other thyroid preparations such as T3 or desiccated thyroid should not be used in pregnancy as the fetal CNS is relatively impermeable to T3.

Assessing Hypothyroidism in Pregnancy
1. Ideally women with hypothyroidism should be seen by their GP pre-pregnancy to ensure that they are euthyroid. They should also be encouraged to present as soon as they become pregnant in order that their thyroxine dose may be increased and TSH and FT4 are monitored regularly. Ideally, TSH should be maintained below 2mU/l. For patients with established hypothyroidism the ideal monitoring regimen is thus:-

- Before conception (if possible)
- At diagnosis of pregnancy or at antenatal booking
- 2 weeks after the dose of T4 has been increased
- At least once in each trimester
- 2-6 weeks postpartum

2. Patients with a history of Graves Disease who are euthyroid or hypothyroid through radioiodine treatment or surgery must have TSH-receptor antibodies (TRAbs) measured early in pregnancy irrespective of the thyroid function test profile.

If TRAbs are undetectable they do not need to be repeated.

If TRAbs are positive the patient will need to be seen by a consultant endocrinologist and consultant obstetrician. It is likely that further measurements of TRAbs will be required in these patients during pregnancy. Patients should be advised to deliver in hospital and the neonatal team must be informed at delivery. Additional ultrasound scans may be required and TSH/FT4/Total T3 on cord blood may be required (see “Managing Hyperthyroidism” section below).

3. Patients newly diagnosed with hypothyroidism whilst pregnant should have T4 treatment commenced immediately with a starting dose of 100 microgram daily. A further assessment of thyroid function tests should be performed after 2 weeks to ensure FT4 is ideally 16-21 pmol/L; TSH should be less than 2 mU/L. Further changes in T4 dose, followed by repeat thyroid function tests may be required to achieve this “ideal” biochemical profile.

- As a minimum, patients should have thyroid function tests performed once each trimester
- If TFTs are unstable refer to a Consultant obstetrician / Consultant Endocrinologist by email as early as possible as growth scans may be required.
- Women with stable, satisfactory thyroid function tests do not need to see an obstetrician but email discussion of TFTs should be initiated by community midwife. An obstetrician will see anyone about whom there are concerns.
- GPs should reduce T4 dose to pre-pregnancy dose at 2-6 weeks post-partum and recheck TSH/Free T4 6-8 weeks later

Subclinical Hypothyroidism and Pregnancy
Subclinical hypothyroidism in pregnancy should be approached as follows:
(a) LT4 therapy is recommended for TPO Ab-positive women with a TSH greater than the pregnancy-specific reference range and for TPOAb-negative women with a TSH greater than 10.0 mU/L.
(b) LT4 therapy may be considered for TPO Ab-positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range or for TPO Ab-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L. This should be discussed with a consultant endocrinologist by sending an ‘Advice Only’ referral on SCI Gateway
(c) LT4 therapy is not recommended for TPOAb-negative women with a normal TSH (TSH within the pregnancy-specific reference range or).

Hyperthyroidism and Pregnancy
Patients being treated with anti-thyroid drugs require careful monitoring during pregnancy as these drugs cross the placenta and interact with the foetal thyroid. Similarly, TSH receptor antibodies (TRAbs) in maternal blood also cross the placenta and may give rise to intrauterine and neonatal thyrotoxicosis if present in high concentration. For these reasons it is essential to identify new cases of Graves’ disease in pregnancy and also to
assess TRAb status in patients with previous Graves Disease who may be hypothyroid or euthyroid due to therapy with radioiodine, surgery or anti-thyroid drugs.

Specialist Management of Hyperthyroidism in Pregnancy

- All women with hyperthyroidism in pregnancy should be seen by a Consultant Endocrinologist and a Consultant Obstetrician from early in pregnancy.
- Home delivery is not appropriate for women with Hyperthyroidism, nor is delivery in the Lothian Birthing Centre as neonatal team review is required in the first 24 hours of life.
- The aim is for good control of hyperthyroidism on the minimum dose of carbimazole (CBZ) / propylthiouracil (PTU) possible. For those with good control of thyrotoxicosis on doses of CBZ<15mg/day or PTU<150mg/day, the maternal and foetal outcome is usually good. The American Thyroid Association recommends use of PTU in the first trimester (to reduce the risk of congenital anomalies) with consideration being given to conversion to CBZ in the second and third trimesters (to reduce the risk of maternal liver dysfunction).

- Any patient with active Graves Disease must have TSH-receptor antibody (TRAbs) measurement carried out at first visit to community midwife (or pre-conception) irrespective of their thyroid function test profile.

Patients with detectable TRAbs
1. The Endocrinologist and Obstetrician should be informed of any patient with detectable TRAbs.
2. Women with detectable TRAb should be advised to deliver in hospital.
3. Further TRAb measurements and ultrasound scans will be required, the frequency of which will be advised by the Endocrinologist and Obstetrician. Typically a scan will be required each trimester, in addition to growth scans at 28 and 34 weeks (more often if control is poor).
4. Paediatricians should be informed of delivery within the first 12 hours of life and the consultant obstetrician will document this in the neonatal management plan during the antenatal period. The infant should be seen within the first 24 hours of life if TRAb are detectable at 36 weeks or if the TFTs from cord blood are abnormal

5. Cord blood should be taken for TSH, FT4 and Total T3 at delivery and the baby should have a resting heart rate checked and remain in hospital for at least 24 hours. Further repeat TSH, Free T4 and total T3 in the neonate should be carried out on the advice of the neonatal team.

CBZ/PTU therapy: Post Natal Management

- The endocrinologist will document a plan for the post natal period as some women will not require CBZ/PTU treatment postnatally. However, all patients should be seen in the Endocrine Clinic 8-12 weeks post partum (or sooner if symptomatic). Vigilance for signs of post natal thyroid storm is essential.
- CBZ is safe in the breast feeding woman in doses at or below 15mg daily and PTU at or below 150 mg daily.

Significance of an “Undetectable” TSH in Pregnancy

Some “normal” pregnancies are associated with a mild transient “physiological” hyperthyroidism during the first trimester. This is caused by very high levels of hCG, which has a mild stimulatory effect on the thyroid. In approximately 3% of pregnancies the TSH will be suppressed to <0.01mU/L and FT4/FT3 may be slightly elevated. It is essential to exclude Graves’ disease in such pregnancies; TRAbs should be measured and an endocrine and/or obstetric opinion sought.

Post-Partum Thyroiditis

This occurs in 5% of women within 2-6 months of delivery or miscarriage. It presents with non-specific symptoms such as tiredness, anxiety and depression. Typically the patient will demonstrate a hyperthyroid hormone profile, which will resolve or be followed by transient hypothyroidism. Occasionally, thyroid function
may not return to normal after postpartum thyroiditis. Persistent hypothyroidism may require treatment with thyroid hormone

- If a hyperthyroid profile is found (TSH <0.01 mU/L; FT4/FT3 raised) an endocrine opinion is warranted to differentiate post-partum thyroiditis from other causes of hyperthyroidism such as Graves’ disease. Measurement of TRAbs will be helpful.

Post-partum patients should have thyroid function tests checked at 8 - 12 weeks if they have:

- Symptoms of hyper or hypothyroidism
- Goitre
- Previous history of post-partum thyroiditis
- Previous history of autoimmune thyroid disease
- Positive TPOAb

References

Original guideline by Dr G Beckett, Dr A Toft, Dr R Hughes & Dr C Calderwood
Updated 2017 by:
Dr C Alexander Consultant Obstetrician
Dr M Crane Consultant Clinical Biochemist
Dr S Forbes Consultant Endocrinologist
Dr N Zammitt Consultant Endocrinologist
Action Points

**Hypothyroidism**

Assess thyroid status: Preferably prior to conception or at booking in the following situations

- Known hypothyroidism
- Type 1, Type 2 diabetes
- Previous history of thyroid disorder
- Family history of thyroid disease
- Features of thyroid disease
- Other autoimmune thyroid disorder

Hypothyroid patients should be offered an appointment with consultant obstetrician

Measure TRAbs in **all** patients with history of Graves’ disease (irrespective of thyroid status). Patients with detectable TRAbs require special management. Inform Endocrinologist/Obstetrician as soon as possible.

Patients with established hypothyroidism should have T4 dose increased by 25 micrograms as soon as a positive pregnancy test is found. Further monitoring after 2 weeks and possible further changes in T4 dose may be required to ensure FT4 is 16-21 pmol/L; TSH <2 mU/L as quickly as possible.

Further checks on thyroid function test should be made at least once in each trimester

*If TFTs are not stable* contact consultant obstetrician, as a growth scan may be required.

Cut back T4 dose to pre-pregnancy dose 2-6 weeks post-partum

**Hyperthyroidism**

All women with hyperthyroidism in pregnancy should be seen by a Consultant Endocrinologist and a Consultant Obstetrician from early in pregnancy

Home delivery is not appropriate for women with hyperthyroidism

Measure TRAbs in **all** patients with Graves’ disease at booking (irrespective of thyroid status). Patients with detectable TRAbs require special management, irrespective of their thyroid function test profile. Inform Endocrinologist and Obstetrician as soon as possible.

The aim is for good control of hyperthyroidism on the minimum dose of carbimazole (CBZ) / propylthiouracil (PTU) possible

**Post-partum Thyroiditis**

Post-partum patients should have thyroid function tests checked at 8 - 12 weeks if they have:-

- Symptoms of hyperthyroidism or hypothyroidism
- Goitre
- History of post-partum thyroiditis or thyroid disease
- Positive TPOAb

If a hyperthyroid profile is found (TSH <0.01 mU/L; FT4/FT3 raised) an endocrine opinion is warranted to differentiate post-partum thyroiditis from other causes of hyperthyroidism such as Graves’ disease. A TRAbs measurement will be helpful for this.
Hypothyroidism in Pregnancy

Newly diagnosed hypothyroid in pregnancy
Start immediately on 100 micrograms T4 daily

Measure FT4/TSH after 2 weeks
Aim: FT4 - 16-21 pmol/L and
TSH less than 2.0 mU/L ASAP
Modify T4 RX and recheck FT4/TSH as required

When stabilised check TSH/FT4
at least once each trimester

Increase T4 dose by 25 micrograms when positive pregnancy test
Check TSH/FT4 after 2weeks

Measure FT4/TSH 2-6 weeks postpartum
Reduce T4 RX as required

Measure TSH/FT4
Before Conception (if possible)
Modify T4 RX - Aim
* FT4 16-21 pmol/L; TSH 0.5-2.0 mU/L

Established treated Hypothyroidism

Modify T4 dose - *Aim
FT4 between 16-21 pmol/L
TSH between 0.5 - 2.0mU/L

Measure FT4/TSH 2-6 weeks post-partum
Reduce T4 dose as required

* It is important to produce this test profile (especially a FT4 of 16-21 pmol/L) as soon as possible in the pregnancy and preferably before conception
Hyperthyroidism in Pregnancy

Pregnant Hyperthyroid?

Active Graves’ disease
Endocrine referral for management Obstetric review by 12 weeks

Previous Graves’ disease or Controlled hyperthyroidism
Monitor TSH/FT4/FT3 Measure TRAbs if known Graves (even if now hypothyroid or euthyroid)
Obstetric review at 28 & 34 weeks Endocrine referral if TRAb positive

Hyperthyroid? TSH < 0.1 mU/L
Low TSH may be due to pregnancy but Graves’ disease must be excluded
Measure FT3, FT4 and TRAbs (NB. pregnancy specific ranges)
If TRAb positive or FT3/FT4 raised seek Endocrine /Obstetric referral