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Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Trust Guideline for:
The Management of Thyroid Disease in Pregnancy

A clinical guideline recommended for use

In:	Maternity
By:	Obstetricians, midwives
For:	Women with Thyroid disease
Key words:	Thyroid, Pregnancy, Hyperthyroid, Hypothyroid, Thyrotoxicosis, Grave's Disease, Thyroiditis, Thyroxine
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INTRODUCTION

Thyroid diseases are the commonest cause of endocrine dysfunction in women of childbearing age and, therefore, encountered commonly in pregnancy. Disorders of thyroid hormone production and their treatment can affect fertility, maternal well-being, fetal growth and development.
Whilst hypothyroidism is common, hyperthyroidism has much greater implications for pregnancy.

THYROID FUNCTION IN PREGNANCY

Thyroid function is altered in pregnancy due to increased metabolic requirements. HCG is also expected to stimulate the Thyroid Stimulating Hormone (TSH) receptor, which leads to an appropriate fall in TSH in the 1st trimester.
Thyroxine binding globulin (TBG) also rises throughout pregnancy which leads to an increase in total T4 levels.. The change in serum free T4 is less obvious, and less consistent, and has been reported variously to rise, fall and be maintained in pregnancy.
Overall then, TSH tends to be lower than usual with a transient rise in free T4 levels during the 1st trimester. TSH then normalises for the rest of pregnancy, and there is a modest fall in Free T4 in 2nd and 3rd trimester, but still within normal ranges; free T3 levels are similar.

REFERRAL PATTERNS FOR MATERNAL MEDICINE [FRIDAY am] ANTENATAL CLINIC

Refer:	**1. History of thyrotoxicosis** **2. History of thyroid carcinoma**
Do not refer	**3. Hypothyrodism – refer to general consultant -led antenatal clinic**

1 + 2 will also be seen by the endocrinologists in the endocrinology clinic and the endocrinologists will monitor the TFTs and prescribe accordingly.

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HYPOTHYROIDISM

In the UK hypothroidism occurs in 2.5% pf all pregnancies, but only 1-3/ 1000 of pregnancies are complicated by overt hypothyroidism. The commonest causes of hypothyroidism are primary hypothyroidism, Hashimoto's thyroiditis , post surgery or post I^{131} therapy. Hashimoto's thyroiditis is associated with thyroid peroxidase antibodies and antithyroglobulin antibodies. Primary hypothyroidism is caused by iodine deficiency however this is less likely in the west due to dietary iodine supplementation.

Overt hypothyroidism causes reduced fertility, and an increased rate of 1st trimester miscarriage. This should therefore be corrected prior to conception. If pregnancy does occur it can be associated with pre-eclampsia, raised BP,and pre-term delivery. Neuropsychological and cognitive impairment have also been reported in infants born to mothers with overt hypothyroidism. Subclincal hypothyrodism refers to an elevated TSH but with a normal free T4. This is more common, but though the risks listed above are lower, they may still be present.

Thyroxine requirements increase in pregnancy in many patients (typically by 30-50%). It is therefore recommended that the pre-pregnancy dose is increase by 25mcg on the diagnosis of pregnancy. This will most likely be in the community however this should be initiated if seeing patients in the 1st trimester e.g. in EPAU.

TFTs should be taken at booking and patients should be seen in a general antenatal clinic (unless the diagnosis follows surgery or treatment with radioiodine).
Aim keep to keep TSH <2 iu.l in patients on replacement therapy. It is not necessary to monitor T4 levels in these patients.
(For women not on treatment, the normal range remains < 3.5iu/l)

TFTs should be checked at each trimester: this can be arranged by writing to the GP. They should be repeated after 6 weeks if the dose is adjusted.
After delivery patients should revert to pre-pregnancy dose and TFTs checked 6 weeks later

HYPERTHYROIDISM

The incidence of hyperthyroidism is 1 in 2000 pregnancies, with virtually all cases due to the autoimmune disease: Graves' disease. Rarer causes include toxic nodules, toxic multinodular goitre, subacute thyroiditis Hashimoto's thyroiditis and trophoblastic disease. Symptoms may improve during pregnancy, and relapse postnatally.
Thyrotoxicosis is confirmed by the finding of a suppressed or undetectable TSH, and elevated free T4/ T3.

The risks of maternal hyperthyroidism are primarily associated with uncontrolled thyrotoxicosis.

Maternal complications of untreated thyrotoxicosis
Heart Failure. Caused by the myocardial effects of T4 and made worse by preeclampsia, infection or anaemia
Thyroid Storm.

Fetal effects
T4 can cross the placenta but its passage is unpredicatable.
T3 and TSH do not usually cross the placenta
Thyroid stimulating antibodies(TRAbs), TRH, TSH receptor antibodies, propyl thiouracil, carbimazole and iodine cross the placenta.
The fetal thyroid axis functions from 10 weeks gestation
After 12 weeks the fetal thyroid concentrates iodine at a higher rate than the maternal thyroid hence iodine should be avoided.

Maternal hyperthyroidism is associated with

Miscarriage
Stillbirth: risk higher if disease presents in pregnancy
IUGR: risk higher if long history of Graves' disease, maternal age < 20 years; poor control
Neonatal thyrotoxicosis occurs in up to 10% of cases of Graves' disease. This is because of transplacental passage of immunoglobulins including thyroid stimulating hormone receptor stimulating antibodies (TRAbs). This condition does not reflect the activity or severity of maternal disease, as the mother may be well controlled by antithyroid drugs, but still have high levels of TRAbs. Neonatal thyrotoxicosis is usually transient, lasting 2-3 months, but is associated with fetal growth retardation, goitre and tachycardia and can be severe. Symptomatic infants need to be transferred to NICU for management. Infants of mothers taking antithyroid drugs in pregnancy may also present late, once the maternal drugs have cleared, but the antibodies are still present in the neonate.

Specific risks associated with Graves' disease and the role of TRAb testing

Graves disease is caused by TSH receptor stimulating autoantibodies: TRAbs. These antibodies can cross the placenta and in theory also stimulate the fetal TSH receptor.

Women on no medication, not treated with surgery or radioactive Iodine

In practise, if the mother no longer requires medication, her TRAbs are likely to be low, and so the fetus is very unlikely to be affected.

Women currently on antithyroid drugs

If the mother currently requires medication, her TRAbs are likely to be high, but since her antithyroid drugs also cross the placenta, the fetus is also likely to be euthyroid. This infant may be at risk of neonatal hyperthyroidism however, as at birth, they will no longer be exposed to antithyroid drugs. Testing this mother for TRAbs late in pregnancy will help define the risk of neonatal hyperthyroidism in this situation.

Women previously treated with Radioactive iodine or surgery

Women who have previously been treated for Grave's disease with surgery or radioiodine, could still have high levels of TSH-receptor antibodies, but because they no longer have viable thyroid tissue, this may not be clinically obvious. Indeed this mother will usually be on thyroxine. Measure TRAbs early in the pregnancy – if they are absent or low levels the risk to the fetus of hyperthyroidism is low. If the levels are high it is necessary to monitor for signs of hyperthyroidism in the fetus and neonate.

Pharmacological agents

Propylthiouracil (PTU) and carbimazole are both used in pregnancy. PTU has a double action, blocking thyroxine synthesis and the conversion of T4 to T3. Carbimazole blocks thyroxine synthesis. Both may have an immunosuppressive effect. Both are associated with side effects in 2-3% of cases, including rash, fever, agranulocytosis (0.2%) and occasional gastrointestinal side effects. Both cross the placenta and can cause transient neonatal hypothyroidism. 'Block and Replace' regimes (of thyroxine plus antithyroid drug) are therefore unsuitable for pregnant women , as the T4 replacement does not predictably cross the placenta.

Because of a possible risk of teratogenicity with carbimazole literature would suggest its avoidance in the 1st trimester. There are no known long term developmental effects with PTU exposure in utero. However, PTU is associated with an increased risk of maternal hepatotoxicity compared to carbimazole.

We therefore recommend that patients seeking pregnancy and throughout the first trimester are treated preferentially with PTU. If they require ongoing treatment with antithryoid drug, this may be switched to carbimazole in the 2nd trimester.
After initial stabilisation the dose is reduced as rapidly as possible (and is frequently withdrawn by the 2nd trimester) to achieve a Free T4 at the upper limit of the normal range (this will be managed in the endocrinology clinc).

Breast feeding
Both appear safe in breast feeding up to doses of 300mg PTU and 15mg carbimazole. Neonatal effects are rare, but infant TFTs should be monitored. Carbimazole is excreted at concentrations equivalent to the maternal circulation. PTU concentration is only 10% of the maternal circulation, and so is preferable in most cases during this period, though again consideration should be given to the higher potential maternal hepatotoxicty with PTU compared to carbimazole.

Radioactive iodine is contraindicated in pregnancy and not advised in the 6 months prior to pregnancy for women (4 months preconception for men).

Surgery for thyrotoxicosis is rarely performed in pregnancy, but is not contraindicated, and is usually best timed in the second trimester.

THYROID STORM (see CA5060Trust Docs)

This **medical emergency** is rare, but can occur in an undiagnosed patient and is usually precipitated by infection, labour or surgery.
Symptoms and signs include:

fever,
tachycardia out of proportion to the fever, normal blood pressure,
high output cardiac failure ,
restlessness, coma, seizures,
gastrointestinal: pain, diarhoea, vomiting

TFTs should be taken prior to treatment and **the endocrinology registrar called. The patient should be admitted to hospital.**
Treatment is with large doses of PTU or carbimazole, potassium iodide or sodium iodide, dexamethasone , propanolol and phenobarbitol. Supportive therapy with iv fluids, oxygen and antipyretics should be administered.

POST PARTUM THYROID DYSFUNCTION

Transient thyroid dysfunction occurs in about 5-10% of women. The incidence is higher in women with existing endocrinological disease, eg IDDM.
Classically there is transient hyperthyroidism, at 6-12 weeks postpartum followed by hypothyroidism. 80% resolve in 6-9 months. Some need long term thyroxine replacement. This should be managed by endocrinologists.

THYROID NODULE & CARCINOMA OF THYROID

Carcinoma of the thyroid may occur in women of childbearing age, and often presents with a thyroid nodule.
Urgent referral should be made to the endocrine clinic.
FNA for cytology of a nodule >1cm should be performed in pregnancy.

Long term thyroxine replacement therapy in the patient with previous thyroid carcinoma is made on an individual case basis but frequently with a suppressed TSH. Pregnant women should be discussed on an individual basis with their endocrinologist/oncologist but a detectable TSH (<0.3) is frequently acceptable during pregnancy.

ANTENATAL MANAGEMENT AND MONITORING

1. Current thyrotoxicosis
Antenatal Clinic: Review in Friday am ANC Monitor for evidence of fetal hyperthyroidism - observe for IUGR – USS 28, 32, 36 weeks growth, consider fetal goitre, document fetal heart rate at USS)
NICU alert
TRAbs last trimester – if high consider increased risk of neonatal hyperthyroidism . Cord blood is not indicated .

Endocrinology clinic: TFTs are taken, reviewed and changes made to medication.
Plan made for postnatal medication and suitability for breast feeding

2. History of thyrotoxicosis treated surgically or with radioactive iodine (i.e. currently euthyroid)

Antenatal Clinic Review in Friday am ANC
TFTs 8 weekly (each trimester) – give forms to patient to have bloods taken a few days prior to next clinic appt.
NICU alert
TRAbs early in pregnancy, if absent or low there is a low risk of fetal hyperthyroidism. They therefore do not need growth scans for this indication
If TRAb levels are high monitor for fetal hyperthyroidism: observe for IUGR – USS 28, 32, 36 weeks growth, consider fetal goitre, document fetal heart rate at USS). Consider at increased risk of neonatal hyperthyroidism.
Cord blood is not indicated .

3. History of thyrotoxicosis treated medically in past (currently euthyroid)

Antenatal Clinic Review in Friday am ANC each trimester
NICU alert
TFTs 8 weekly (each trimester) – give forms to patient to have bloods taken a few days prior to next clinic appt.
If euthyroid, no additional scans required, plus low risk of neonatal thyrotoxicosis low. TRAbs not indicated

4. History of thyroid carcinoma

Antenatal Clinic Review in Friday am ANC
Endocrinology clinic Review in separate Endocrinology clinic where TFTs are reviewed. Need documented target TSH on an individual basis bearing in mind the relative risks of maternal biochemical thyrotoxicosis v cancer risk. General aim is to keep TSH suppressed but detectable.

HYPEREMESIS GRAVIDARUM

Measure TFTs in all patients with hyperemesis on 1st admission.
HCG has a weak thyroid-stimulating activity as it is a glycoprotein hormone with a common alpha sub-unit to TSH. 10-20% normal women will have a TSH that is low or undetectable in the 1st trimester.
Treat overt hyperthyroidism only, not an isolated low TSH: elevated free T4 above reference range and clinical evidence. Consider use of thyroid antibody screen and TRAbs to differentiate between hyperemesis and maternal Graves'.
Refer to joint antenatal obstetric / endocrine clinic for further management.
As per hyperemesis guidance ensure single viable intra-uterine pregnancy as high levels HCG associated with molar pregnancy and twins.

SCREENING

Women with type I diabetes are at increased risk of thyroid disease and should be screened in early pregnancy –this can be performed in the joint diabetic antenatal clinic.

How to order TRABS
On ICE use search box, search on receptor .

Auditable standard

The Maternity Services are committed to the philosophy of clinical audit, as part of its Clinical Governance programme. The standard contained in this clinical guideline will be subject to continuous audit, with multidisciplinary review of the audit results at one of the monthly departmental Clinical Governance meetings. The results will also be summarised and a list of recommendations formed into an action plan, with a commitment to re-audit within three years, resources permitting.

Standards

1. Women with history of Thyrotoxicosis having TFT in each trimester
2. Women with history of Thyroxicosis having TRAb as per guideline

3. Women with Hypothyroidism for whom the pattern of care has been communicated to the GP

4 Women with thryrotoxicosis having fetal moinitoring as per guideline

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