GUIDELINE FOR MANAGEMENT OF THYROID DISORDERS IN PREGNANCY

Document Author: Nicholas Oriaifo

Approved by: Antenatal Forum/Clinical Guideline Group

Approval Date: 23rd September 2024

Review Date: September 2027

Document No: 1

Contents

Summary
Although uncommon, thyroid disorders are important endocrine conditions that can be encountered in pregnancy.

Hyperthyroidism or thyrotoxicosis:

- 90% of cases are due to Graves' disease.
- Symptoms include heat intolerance, tachycardia, palpitations, palmer erythema, emotional lability, vomiting, swelling of the thyroid gland (goitre), weight loss, tremors.
- Diagnosis usually made outside pregnancy and most pregnant women will have already had some treatment.
- Preconception care is aimed at achieving a euthyroid state, discontinuing potentially harmful treatment including radioiodine, propranolol. Also, antithyroid drugs should be on minimal maintenance dose prior to consideration of conception.
- Pregnancy should be avoided for 4 months following use of radioiodine.
- Antenatally, antithyroid medications should be continued on usual dose.
- Womens should be aware of potential risks with individual medications. Switching from Carbimazole to PTU is not routinely done.
- When control is maintained on antithyroid drugs, thyroid function should be repeated 4-6 weekly. Also, a full blood count and liver function test (for Womens on PTU) should be performed alongside TFT due to risk of agranulocytosis and liver failure.
- Serial growth scans are indicated for Women with TRAb antibodies, on antithyroid drugs and/or on propranolol. Scans may also be indicated for other obstetric or medical indications.
- In periods of stress like during labour, surgery (Caesarean section) or infections, patients should be closely monitored due to the risk of developing potentially life threatening thyrotoxic crisis, that required urgent multi-disciplinary management.
- Bloods should be repeated 4 – 6 weeks post-partum and adjustment or recommencement of medications may be required.

Hypothyroidism

- Most cases are autoimmune in nature. May also occur following previous treatment for hyperthyroidism.
- Most women are diagnosed prior to pregnancy and already on replacement therapy with thyroxine.
- Preconception care is aimed at ensuring a euthyroid state prior to conception.
- Women that are euthyroid prior to conception should be continued on their usual dose of thyroxine.
- Routine dose increases in early pregnancy are not recommended.
- TSH is used to monitor control and should be maintained below 2.5mIU/L. Test should be performed once in each trimester when control is good or 4 weeks after dose adjustments.

- Serial growth scans are indicated for women in whom diagnosis was made in pregnancy and when achieving euthyroid state is difficult or when compliance to medications is poor or for other obstetric or medical indications. Otherwise, women can be under Midwifery led care for monitoring of TSH levels.
- Women require not further monitoring in the third trimester if thyroid function has been optimal until then.
- Bloods should be repeated 4-6 weeks postpartum as dose adjustments may be required.

Introduction

Thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) are essential for

- Stimulation of basal metabolic rate
- Maintenance of cardiac contractility and rhythm, through effects on the autonomic nervous system
- Normal neurological development
- Synthesis and secretion of growth hormone

Normal thyroid hormone synthesis and secretion is maintained by the hypothalamic-pituitary-thyroid axis in a concert of feedback and feedforward mechanisms involving thyroid releasing hormone (TRH) and somatostatin from the hypothalamus, thyroid stimulating hormone (TSH) from the pituitary and T3 and T4 from the thyroid gland. Thyroid hormone disorders could be excessive synthesis and secretion of thyroid hormones or their deficiency. These disorders are commoner among women in their reproductive years than their male counterparts and hence are commonly encountered in pregnancy.

Physiologic changes in pregnancy are associated with an alteration in thyroid hormone milieu and this should be considered in interpreting blood results. In the absence of an abnormality however, normal thyroid function is maintained.

Physiological Changes in Pregnancy

- Increase in size and vascularity of the thyroid gland.
- Increase in hepatic secretion of thyroid binding globulin (TBG)

These effects tend to occur in the first and early second trimester, with a steady achieved by the third trimester. The result is increased secretion of T3 and T4. While the total levels may be elevated, the free levels remain within normal. Hence trimester specific values should be used for interpretation of thyroid function tests in pregnancy.

Table: 1

	Non-Pregnant	**First Trimester**	**Second Trimester**	**Third Trimester**
TSH (mIU/L)	0 – 4.0	0.1 – 1.6	0.1 – 1.18	0.7 – 7.3
T3 (pmol/L)	4 - 9	4 - 8	4 - 7	3 - 5
T4 (pmol/L)	11 - 23	11 - 22	11 - 19	7 - 15

The thyroid disorders encountered in Pregnancy Include:

- Hyperthyroidism
- Hypothyroidism
- Post Partum Thyroiditis

Hyperthyroidism (Thyrotoxicosis)
This mostly autoimmune condition affects 1:500 pregnancies. Fortunately, most cases are already diagnosed and on treatment prior to pregnancy.

Clinical Features
May be confused with physiological changes of pregnancy and include heat intolerance, tachycardia, palpitations, palmer erythema, emotional lability, vomiting, swelling of the thyroid gland (goitre).

Thyrotoxicosis is however differentiated by the presence of weight loss, tremors, persistent tachycardia, lid lag and exophthalmos. If thyrotoxicosis occurs for the first time in pregnancy, it usually does in the first or early second trimester.

Pathogenesis
>90% of cases of thyrotoxicosis encountered in pregnancy are due to Grave's disease which itself is an autoimmune disorder caused by Thyroid stimulating hormone (TSH) receptor stimulating antibodies.

Other less common causes include toxic goitres, toxic thyroid adenomas, acute or subacute thyroiditis, drugs (iodine, amiodarone, lithium).

Effects of Pregnancy on Thyrotoxicosis
Pregnancy is associated with a relative immunosuppression, which leads to a fall the TSH levels that leads to improvement of graves diseases and reduction in requirement for treatment during pregnancy. This usually occurs in the second/third trimesters.

In the first trimester/ early second trimester and in the puerperium however, there may be exacerbation of symptoms related to human chorionic gonadotrophins (hCG) and reversal of the pregnancy related fall in antibody levels respectively.

Pregnancy has no effect on thyroid ophthalmopathy, making it an important distinguishing feature, when thyrotoxicosis is encountered for the first time in pregnancy.

Effects of thyrotoxicosis on Pregnancy
Severe untreated thyrotoxicosis results in anovulation and subfertility however, for those who become pregnant and remain untreated, pregnancy is associated with increased risks of miscarriage, fetal growth restriction, preterm labour, and perinatal mortality.

Thyroid stimulating antibodies can cross the placenta and cause fetal thyrotoxicosis.

Maternal thyrotoxicosis may result in sinus tachycardia, supraventricular tachycardia, or atrial fibrillation. If poorly controlled a thyroid crisis (storm) and heart failure may result, and this is more common at the time of delivery.

Well controlled thyrotoxicosis on anti-thyroid drugs or previously treated Graves' disease in remission is associated with good maternal and fetal outcomes.

Diagnosis
Diagnosis is made by the finding of an elevated free thyroxine (T4) and triiodothyronine (T3) above the normal range for the gestational age. This is usually associated with suppression of TSH. However, a low TSH level should not be used in isolation for making a diagnosis.

It is important to use ranges specific for each trimester of pregnancy as some of these changes may occur normally in pregnancy.

There is no evidence to support routine screening in pregnancy and testing should be directed by clinical features as described above.

Management
The aim of management is to achieve and maintain a euthyroid state. This is achieved in different ways; however, options are limited in pregnancy.

Preconception
Outside pregnancy, several options are available for treatment with the same aim of achieving and maintaining a euthyroid state. Treatment modalities include:

- Antithyroid drugs
- Beta Blockers
- Surgery
- Radioactive iodine

Antithyroid drugs
- Carbimazole and Propylthiouracil are the commonly used drugs in this class.
- Usually commenced at doses of 15 – 40mg carbimazole (150 – 400mg PTU) for 4- 6 weeks.
- The onset of action of antithyroid drugs is delayed for 3-4 weeks (depletion of preformed hormones).
- The dose is then gradually reduced to a maintenance of 5-15mg (50 -150mg PTU), and treatment is continued for 12 to 18 months.
- Remission is expected at this time although relapses and common and treatment for relapsed include long term use of anti-thyroid drugs (which is recommended for women considering a pregnancy), surgery or radioiodine.
- Both medications can cross the placenta, with a 2-4% risk of fetal congenital anomalies (Carbimazole > PTU). This risk should be discussed with women and a switch from Carbimazole to PTU should be made preconceptionally if considered.

Beta Blockers

- Propranolol is the commonly used agent in this class of drugs.
- They are used in early management of thyrotoxicosis, for control of sympathetic symptoms of palpitations, tremors, sweating.
- They are discontinued once euthyroid state is achieved.
- Doses as high as 40mg 3 times a day for 3-4 weeks are not considered harmful to the fetus.

Surgery:

- Indicated for cases of recurrent remissions or in the presence of a large goitre with obstructive symptoms.
- Following surgery, hypothyroidism is common, and maintenance is usually required.
- Euthyroidism should be achieved and maintained prior to contemplating a pregnancy.

Radioiodine

- Effective treatment for recurrent remissions.
- Is however contraindicated in pregnancy and breastfeeding.
- Pregnancy to be avoiding for at least 4 months following treatment.
- It is also important to commence replacement if required following treatment and achieve euthyroidism prior to contemplating pregnancy.

Antenatal

- All women with known thyroid disorders should be referred to the Obstetric Medicine clinics following their booking appointments in accordance with their geographical abode i.e., Singleton, Neath or Llanelli.
- Women on antithyroid drugs who are euthyroid in early pregnancy should be continued on the same medication and dose through pregnancy.
- Dose adjustments should be guided by thyroid function tests which should be performed 4-6 weekly through pregnancy.
- Thyroid stimulating hormone receptor antibodies (TRAb) should be tested for in early pregnancy as their presence indicates active Graves' disease and is associated with an increased risk of fetal growth restriction and fetal Graves' disease.
- Routine switch from carbimazole to PTU is not encouraged however, women should be informed of the relative risks of both medications.
- Use of beta-blockers should be guided by Women's symptoms.
- Serial growth scans with umbilical artery doppler and liquor volume assessment should be performed from 26-28 in the presence of TRAb antibodies or use of antithyroid drugs in pregnancy. For women with a previous history of Graves' disease, not requiring treatment in pregnancy and are TRAb antibody negative, fetal surveillance with serial scans is not indicated.
- Newly diagnosed thyrotoxicosis in pregnancy requires initial treatment with high doses; 45-60mg of carbimazole (450 -600mg PTU) for 4 to 6 weeks, and then a gradual dose reduction, aiming to maintain a euthyroid state on the lowest required dose, usually at or below 15mg per day of carbimazole (150mg PTU).

- Women with Graves' disease may require lower doses as pregnancy advances and as much as 30% of previously treated women require no medication in the last trimester. This is due to the relative immune suppression of pregnancy, a condition that reverses post-partum and could be associated with a relapse. A review of thyroid function should be performed 4 – 6 weeks and at this time doses may me increased or medication reintroduced if previously discontinued. This should be organised by the GP and planned at the last antenatal appointment.

Intra partum

- Timing and mode of delivery should be determined by obstetric factors.
- However, as labour is a period of increased physiologic stress, women are at risk of developing thyrotoxic crisis.

Thyrotoxic Crisis (Thyroid storm)

- It is a medical emergency that is potentially life threatening.
- It results from an abrupt surge in thyroid hormone synthesis, resulting from antibody stimulation of the gland.
- Associated with periods of increased physiologic stress like labour. Other potential triggers are surgery, infections, abrupt discontinuation of medications.
- Clinical features include congestive cardiac failure, hyperpyrexia, dysrhythmias, altered mental state, in addition to other features of thyrotoxicosis which are typically exaggerated.
- Urgent multidisciplinary care is required for management, and this involves intravenous fluids (careful administration in the presence of cardiac complications), high dose of propranolol and hydrocortisone, antithyroid drugs. Subsequent care is supportive and may be in the intensive care unit, depending on response to initial treatment.
- Women should be closely monitored in the presence of risk factors for thyroid storm, and compliance with antithyroid drugs ensured.

Post Natal

- Neonatal glycaemic monitoring should be performed if propranolol was used in pregnancy.
- Thyroid function test +/- antithyroid dose adjustment at 4-6 weeks post-partum.
- Thyrotoxicosis does not affect contraceptive use; however, doses should be adjusted with the use of the combined contraceptive pill.

HYPOTHYROIDISM

Complicates ~1% of pregnancies.

Most cases already diagnosed and on treatment prior to pregnancy.

Clinical Features
Symptoms are similar to some symptoms encountered in normal pregnancy and include weight gain, lethargy, somnolence, hair loss, dry skin, constipation, carpal tunnel syndrome, fluid retention.

The presence of cold intolerance, relative bradycardia, delayed relaxation of tendon reflexes should prompt clinical suspicion of hypothyroidism.

Commonly associated with other autoimmune conditions including pernicious anaemia, Type 1 diabetes mellitus, which may be of clinical importance in pregnancy.

Pathogenesis
Most cases result from autoimmune destruction of the thyroid gland by microsomal autoantibodies.

There are 2 principal sub-types: Atrophic thyroiditis and Hashimoto's thyroiditis. The latter is the name given to the combination of autoimmune thyroiditis and goitre.

Hypothyroidism may be iatrogenic following radioiodine therapy, surgery or related to drugs (amiodarone, lithium, antithyroid drugs). Transient hypothyroidism may be found in subacute (de Quivain's) thyroiditis and in postpartum thyroiditis.

The commonly encountered forms are Hashimoto's thyroiditis and Iatrogenic following treatment of Graves' disease.

Diagnosis
- Routine testing in pregnancy is not recommended.
- Testing should be guided by clinical features.
- Most cases however are diagnosed prior to pregnancy.
- In pregnancy the TSH and Free T4 levels should be checked. Thyroid autoantibodies (TPO) should be tested in newly diagnosed cases or where there is a relapse of previously treated disease.
- Diagnosis is made by finding a low level of free T4. Normal pregnant ranges for each trimester should be used. Cases where a low free T4 is accompanied by an elevated TSH are referred to as Overt hypothyroidism and in cases where TSH is elevated in isolation, it is termed subclinical hypothyroidism.
- The finding of thyroid autoantibodies supports diagnosis but should not be used in isolation as they are present in 20 – 50% of population.

Effects of Pregnancy on Hypothyroidism
- 25% of previously treated women will require an increase in their replacement doses.
- Pregnancy does not otherwise affect hypothyroidism.

Effects of Hypothyroidism on Pregnancy
- If severe and untreated, is associated with anovulation, amenorrhoea, and subfertility.

- Those who become pregnant and remain untreated are at increased risk of miscarriages, anaemia, late pregnancy loss, preeclampsia, small for gestational age (SGA).
- Baby's born are at increased risk of reduced intelligent quotient and neurodevelopmental delay. Severe cases of maternal iodine deficiency may result in permanent fetal/ neonatal brain damage, cretinism.
- Women on adequate replacement and are euthyroid in early pregnancy have good outcomes and pregnancy is unaffected by hypothyroidism.

Management

- All women with Known thyroid disease should have their thyroid function tested in the first trimester. Dose adjustments for levo-thyroxine should be made inaccordance with TSH levels.
- All women requiring dose adjustments and newly diagnosed cases a referral should be made to the Obstetric medicine clinic for joint Consultant Obstetrician and Endocrinology care.
- When hypothyroidism is clinically suspected, TSH, free T4 and TPO should be tested, and women should be referred if results fall outside of the gestational age specific reference ranges.
- Most women are already on maintenance doses of thyroxine prior to conception.
- Women should be reassured that only small amounts cross the placenta and hence it is safe to continue in pregnancy.
- Adequate replacement should be ensured prior to conception by checking thyroid function and titrating doses as required.
- Thyroxine is preferably taken on an empty stomach. Absorption is impaired by coadministration with Iron and calcium supplements, and this should be avoided.
- A thyroid function test should be repeated in early pregnancy. Routine testing for TPO antibodies is not recommended for women already diagnosed and on thyroxine replacement.
- Women who remain euthyroid in early pregnancy do not require routine adjustment of their thyroxine doses.
- Thyroid function should be checked 4-6 weekly through pregnancy.
- Levothyroxine doses should be increased when TSH levels are >2.5 mIU/L.
- Following any adjustment in dose, thyroid function should be checked after 4 weeks.
- Isolated raised TSH is common in early pregnancy, and adjustment dose of thyroxine at this time must be justified by low free T4 or persistently raised TSH in the presence of normal T4 (subclinical hypothyroidism). Thyroid function test should be repeated after 4 weeks if isolated low free T4 is found in the first trimester.

- New diagnosis of hypothyroidism in pregnancy is uncommon. When this is the case, replacement with thyroxine should be commenced immediately. In the absence of cardiovascular disease, 100mcg daily is recommended as a starting dose and thyroid function rechecked after 4 weeks. However, if cardiovascular disease is present, 50mcg daily should be initially commenced and dose adjusted as appropriate.
- Fetal surveillance with serial scans for growth, liquor volume and umbilical artery doppler from 28 weeks is indicated in the presence of poor control, or new diagnosis in pregnancy. Additional fetal surveillance or Obstetric intervention is not recommended in the presence of good control of thyroid function. Women do not require further testing in the third trimester if thyroid function has been optimal.
- For women who had dose adjustments in pregnancy, thyroid function test should be repeated at 4-6 weeks post-partum to determine if the dose of thyroxine needs to be readjusted.

SUBCLINICAL HYPOTHYROIDISM

- This term describes a condition of persistently high TSH and normal free T4 in the absence of symptoms of hypothyroidism.
- Commoner in women with thyroid antibodies.
- Thers is some evidence for increased risk of adverse pregnancy outcome with this condition including preterm delivery, placental abruption. There is however no evidence to suggest that treatment with thyroxine improves outcome.
- Women known to be antibody positive or those previously known to have subclinical hypothyroidism should have their thyroid function checked preconceptionally and in early pregnancy.
- A rising TSH or falling free T4 is indication for commencement of treatment with thyroxine. Starting dose for thyroxine treatment of subclinical hypothyroidism is 25 – 50mcg daily. Treatment should not be commenced if TSH remains within 2.5 – 4mU/L.

POSTPARTUM THYROIDITIS

- Transient autoimmune mediated thyroid dysfunction occurring within 6 months of delivery.
- Associated with the presence of anti-thyroid antibodies.
- Women will usually have a family history of hypothyroidism.

Clinical Features

- Could be monophasic in which case hypothyroidism or hyperthyroidism occurs within months of delivery or biphasic, in which case an initial period of hyperthyroidism is followed by a prolonged (>6months) period of hypothyroidism.
- Non-specific symptoms which depend on the phase. However, a painless goitre is present in up to 50% of cases.

Pathogenesis

- May represent an activation of previously subclinical thyroiditis.
- Autoimmune mediated thyroid gland inflammation results in release stored thyroid hormones. This results in symptoms of hyperthyroidism.
- Hypothyroidism results from depletion of thyroid stores.
- Resolution is usually spontaneous.

Diagnosis and Management

- This condition is often overlooked as the symptoms are mostly mild and non-specific, and resolution is spontaneous.
- Short term treatment with levothyroxine may be indicated in some cases.
- It is however important to exclude Grave's disease, for which treatment with antithyroid drugs is indicated. This distinction is made by testing for Thyroid stimulating antibodies which are present in Graves' disease and absent in post-partum thyroiditis.

References

Abalovich, M., Amino, N., Barbour, L.A., Cobin, R.H., De Groot, L.J., Glinoer, D., Mandel, S.J., Stagnaro-Green, A., 2007. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol. Metab*. 92, s1–s7. https://doi.org/10.1210/jc.2007-0141

Abbassi-Ghanavati, M., Greer, L.G., Cunningham, F.G., 2009. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet. Gynecol*. 114, 1326–1331. https://doi.org/10.1097/AOG.0b013e3181c2bde8

Alexander, E.K., Pearce, E.N., Brent, G.A., Brown, R.S., Chen, H., Dosiou, C., Grobman, W.A., Laurberg, P., Lazarus, J.H., Mandel, S.J., Peeters, R.P., Sullivan, S., 2017. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid 27, 315–389*. https://doi.org/10.1089/thy.2016.0457

Cotzias, C., Wong, S.-J., Taylor, E., Seed, P., Girling, J., 2008. A study to establish gestation-specific reference intervals for thyroid function tests in normal singleton pregnancy. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 137, 61–66. https://doi.org/10.1016/j.ejogrb.2007.10.007

De Groot, L., Abalovich, M., Alexander, E.K., Amino, N., Barbour, L., Cobin, R.H., Eastman, C.J., Lazarus, J.H., Luton, D., Mandel, S.J., Mestman, J., Rovet, J., Sullivan, S., 2012. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol.* Metab. 97, 2543–2565. https://doi.org/10.1210/jc.2011-2803

Donhorst A, Williamson C, 2007. Diabetes and endocrine disease in pregnancy, Edmunds DK. *Dewhurst's Textbook of Obstetrics and Gynaecology*. Blackwell Publishers, 7th edition, 2007. pp 246 - 60.

Dhillon-Smith, R.K., Boelaert, K., Jeve, Y.B., Maheshwari, A., Coomarasamy, A., Royal College of Obstetricians and Gynaecologists, 2022. Subclinical hypothyroidism and antithyroid autoantibodies in women with subfertility or recurrent pregnancy loss: Scientific Impact Paper No. 70 June 2022. BJOG Int. J. Obstet. Gynaecol. 129. https://doi.org/10.1111/1471-0528.17187

Girling, J., 2008. Thyroid disease in pregnancy. *Obstet. Gynaecol. 10, 237–243*. https://doi.org/10.1576/toag.10.4.237.27440

Girling, J., Nelson-Piercy, C., 2007. Three unresolved issues. *BMJ 335, 362.1-362*. https://doi.org/10.1136/bmj.39311.457627.3A

Kothari, A., Girling, J., 2008. Hypothyroidism in pregnancy: pre-pregnancy thyroid status influences gestational thyroxine requirements. *BJOG Int. J. Obstet. Gynaecol.* 115, 1704–1708. https://doi.org/10.1111/j.1471-0528.2008.01901.x

Nelson-Piercy C. Thyroid and Parathyroid disease. *Handbook of Obstetric Medicine, 6th edition*. CRC press, 2020. pp 106-24

Maternity Services
Checklist for Clinical Guidelines being Submitted for Approval

Title of Guideline:	GUIDELINE FOR MANAGEMENT OF THYROID DISORDERS IN PREGNANCY
Name(s) of Author:	Nicholas Oriaifo
Chair of Group or Committee approving submission:	Clinical Guideline Group
Brief outline giving reasons for document being submitted for ratification	New policy
Details of persons included in consultation process:	Antenatal Forum Clinical Guideline Group
Name of Pharmacist (mandatory if drugs involved):	n/a
Issue / Version No:	1
Please list any policies/guidelines this document will supercede:	n/a
Date approved by Group:	23rd September 2024
Next Review / Guideline Expiry:	September 2027
Please indicate key words you wish to be linked to document	Thyroid, pregnancy,
File Name: Used to locate where file is stores on hard drive	ABM Group (Z:)\Maternity\policies and guidelines\Obs\2020 onwards