GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Cwm Taf Morgannwg University Health Board

Management of Maternal Thyroid Disorders During Pregnancy

Initiated By	Cwm Taf Morgannwg University Health Board Obstetrics and Gynaecology Directorate
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Version	Date	Author Job Title	Reasoning
1.0	March 2020	Mr Ken Emmanuel Consultant Gynaecologist	
1.1	December 2020	Mr Ken Emmanuel Consultant Gynaecologist Dr Daniel Adama ST1 Obstetrics and Gynaecology	Comments about iodine supplementation and references.

AUTHORSHIP, RESPONSIBILITY AND REVIEW

Author	Mr Ken Emmanuel	**Ratification Date**	March 2020
Job Title	Consultant Gynaecologist	**Review Date**	March 2023
Service Group	Women and Child Health	**Clinical Director**	Miss Jo Hilborne
Service Lead	Clinical Director	**Directorate Manager**	Mr Tarek Allouni

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BACKGROUND

Guideline Definition

Clinical guidelines are systemically developed statements that assist clinicians and patients in making decisions about appropriate treatments for specific conditions.

They allow deviation from a prescribed pathway according to the individual circumstances and where reasons can be clearly demonstrated and documented.

Purpose

To assist medical and nursing staff in the management of maternal thyroid disorders in pregnancy.

Many complaints come from poor communication and contradictory advice.

The guideline aims to minimise this by standardising the information, advice and treatment that we provide to those couples who suffer early pregnancy loss and require medical treatment.

Scope

For all staff, medical, nursing and clerical, to provide uniformity in the management of patients diagnosed with a first trimester miscarriage.

Roles and Responsibilities

In seeking further advice on any uncertainties contained in this document, or if you feel that there is new or more updated advice it is your responsibility to contact the guideline author or Approval Group manager so that any amendments can be made.

The guideline Approval Group is responsible for disseminating this guideline to all appropriate staff.

The guideline author or a named alternative is responsible for updating the guideline with any amendments that they become aware of or are highlighted to them.

All health professionals are responsible to ensure that the guideline is utilised effectively, and to ensure that they are competent and compassionate in the implementation of it.

Training Requirements

There is no mandatory training associated with this guideline.

Monitoring of Compliance

- By audit and review of complaints relating to miscarriage diagnosis and management.
- The Governance Department will collate any complaints and distribute to the relevant individuals for comments, and share any learning points.
- The Service Lead will oversee any governance issues, make relevant recommendations to the directorate, and advise the Clinical Director or the directorate of any matters that require implementation.
- The Health Board reserves the right, without notice, to amend any monitoring requirements in order to meet any statutory obligations or the needs of the organisation

Complaints

All complaints should try to be resolved with the patient during any contact to avoid escalation. There concerns should be listened to and documented. If it is not possible to address any concerns at the time, or if the complaint is of a serious nature, the patient's complaint should be discussed with the consultant in charge for the day, or the patient should be given details of how to raise a formal complaint via the local governance department.

Related Guidelines

- Wales Neonatal Network Guideline. Management of Neonates Born To Mothers with Thyroid Disease (June 2018)

Definition and Background

Thyroid disease is common, affecting 1% to 2% of pregnant women. Pregnancy may modify the course of thyroid disease, and pregnancy outcomes can depend on optimal management of thyroid disorders. Consequently, obstetric providers must be familiar with thyroid physiology and management of thyroid diseases in pregnancy. Recommendations for screening and treatment of hypo- and hyperthyroidism are summarized.

Early diagnosis and good management of maternal thyroid dysfunction is essential to ensure minimal adverse effects on fetal development. 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 done for screening purposes or to check thyroid status in patients with established thyroid disorders is more likely to be done by the GP.

Women with untreated hypothyroidism or hyperthyroidism rarely become pregnant. Hypothyroid women on treatment may need their dose adjusting. A good outcome is expected.

Safety Net Advice and Urgent Referral

- Refer any woman with overt signs of thyroid disease immediately to an endocrinologist or obstetrician for urgent review.

GENERAL MANAGEMENT

Responsible Clinician

Women with thyroid disease should be referred to one of the following specialist person(s) for ongoing care in pregnancy:

- a joint endocrine/antenatal clinic (preferred)
- an obstetrician with an interest on maternal medicine (preferred)
- an obstetrician skilled in the management of thyroid disease

Women at Risk of Thyroid Disease

Healthy women of reproductive age do not need to be screened for subclinical thyroid disease.

The following women should be screened for thyroid disease using TSH and FT4, preferably prior to conception, or at the earliest opportunity in the pregnancy:

- Type 1 and Type 2 diabetes or past gestational diabetes
- Any history of autoimmune disorders e.g. coeliac disease, etc
- Previous, current history, or family history (1st degree relative) of thyroid disease
- Family history of thyroid disease (1st degree relative)
- Goitre or other clinical features of thyroid disease
- Use of lithium, amiodarone or recent treatment of overactive thyroid
- Molar pregnancy
- Age 30+

Blood Testing

Method, population and trimester-specific reference ranges for TSH and FT3/FT4 should be requested from the laboratory in order to make a diagnosis of thyroid disease.

Free T3/T4

Maternal FreeT4 (FT4) and Free T3 (FT3) rather than total hormone concentrations must be measured in pregnancy. It is only FT3/FT4 that than can enter cells and modify metabolism.

TSH

A TSH < 4.0mU/L should be considered to be normal in pregnancy after 7 weeks of gestation (prenatally <3.5). However, a cut-off value of 2.5-3.0 is commonly used but may result in overtreatment of women.

TSH 2.5-5.0 is associated with miscarriage rates of 6.1% compared to 3.6% when TSH < 2.5.

Iodine Supplementation

The recommended iodine intake during pregnancy and lactation is 250 mcg daily (150mcg non-pregnant). The common pregnancy supplements (e.g. Pregaday, Seven Seas, etc.) provide 100-150mcg of iodine daily. This may be further supplemented by over-the-counter supplements such as in Sea Kelp, to achieve the recommended daily dose.

HYPOTHYROIDISM

Diagnosis

- Elevated TSH with low FT4 **or** TSH≥10 with low/normal FT4
- Sub-clinical disease can exist with mildly elevated TSH and normal thyroxine levels.

Obstetric Risks

If hypothyroidism is well controlled pregnancy complications are unlikely. In pregnancy there is an increased requirement for thyroxine.

Subclinical Hypothyroidism (SCH)

SCH been associated with subfertility and poor pregnancy outcomes including increased risk of **miscarriage, preterm delivery, pregnancy induced hypertension, gestational diabetes, growth restriction and premature rupture of membranes**. Women who are TPOAb positive (marker of auto-immune thyroid disease) have increased rates of miscarriage and preterm delivery independent of thyroid function.

If hypothyroidism is sub-optimally treated, there is an increased risk of preterm labour, pregnancy induced hypertension, placental abruption, anaemia, postpartum haemorrhage, and impaired fetal intellectual development due to low FT3/FT4 levels as early as 5 weeks' gestation. Thus, it is very important to ensure adequate thyroxine replacement as early as possible in pregnancy, ideally prenatally.

There is an increase in serum free thyroxine (FT4) levels in women early in normal pregnancy. However, in women with hypothyroidism this increase does not occur.

The fetus relies on maternal thyroxine until 12 weeks' gestation when its own thyroid gland develops.

Obstetric Care

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

If the thyroid function testing remains stable, ongoing care can be managed by the community midwife and GP.

Ideally women with hypothyroidism should be seen pre-pregnancy to ensure that they are euthyroid. They should also be encouraged to present as soon as they become pregnant in order that:

- Thyroxine dose may be:
    - commenced at 2mcg/kg for (max 100mcg) for overt hypothyroidism (TSH>10), or
    - commenced at 1mcg/kg for subclinical hypothyroidism (max 50-75mcg)
    - increased by 30% (or minimum of 25mcg) for pre-existing
- TSH and FT4 are monitored regularly.

Monitoring

If the woman's serial thyroid testing remains stable, ongoing thyroid function testing is usually managed by the GP and supported by the community midwife.

Fetal Monitoring

Growth scans are 28, 32 and 36 weeks due to the risks associated with hypothyroidism. More scans may be required if the thyroid disease is poorly controlled.

Subclinical Hypothyroidism (SCH)

If the TSH level is 2.5mIU/L or more on early pregnancy screening, levels of anti-thyroid peroxidase antibodies (TPOAb) should be measured to identify women who may benefit from treatment for SCH.

KEY MESSAGE:

- **Subclinical hypothyroidism is a milder, more common form of hypothyroidism and is defined as an elevated TSH level (4.0-10) with a normal free T4 level.**

Blood Testing During Pregnancy

For patients with suspected, past or established hypothyroidism arrange thyroid function testing as follows:

- Organise thyroid function test (TFT) at booking or by 6-8 weeks' gestation, then every 6-8 weeks until 36 weeks.
    - **If TSH>2.5 check TPOAb**
- Repeat TFT 4 weeks after adjusting the dose of levothyroxine.
- Repeat TFT's 4-8 weeks after delivery and adjust levothyroxine dose accordingly (usu. to pre-pregnancy levels).
- If TFTs unstable refer to a consultant endocrinologist or obstetrician as early as possible.

KEY MESSAGE:

- **Aim for a post treatment TSH of 2.0 during the course of the pregnancy**

Drug Therapy

Levothyroxine (T4) dosing depends on TFT's. An increase in levothyroxine dose is likely by an average of 25-50 mcg as pregnancy progresses.

Expect T4 requirements to increase by up to 50% by 20 weeks and then plateau.

- **Patients with established hypothyroidism**:
    - Daily levothyroxine dose should be **increased by 30%, or a minimum of 25 micrograms**, when the pregnancy is confirmed.
    - Thyroid function tests should be re-checked after approximately 2 weeks to ensure that a satisfactory FT4 level has been achieved:
        - FT4 16-21pmol/L with ideally TSH of less than 0.5-2 mU/L
    - A further increase in T4 dose every 2-4 weeks may be required to achieve the above levels.

- **Patients newly diagnosed with hypothyroidism whilst pregnant:**
    - Daily levothyroxine treatment commenced immediately **with a starting dose of 2mcg/kg (max 100 microgram daily), or 1mg/kg (max 50-75mcg) for SCH**.
    - Thyroid function tests should be re-checked after approximately 2 weeks to ensure that a satisfactory FT4 level has been achieved:
        - FT4 16-21pmol/L with ideally TSH of less than 0.5-2 mU/L
    - A further increase in T4 dose every 2-4 weeks may be required to achieve the above levels

HYPERTHYROIDISM

Diagnosis

- Elevated FT4
- Elevated FT3
- Suppressed TSH to less than 0.02
- TSH Receptor Antibodies (TRAbs): specific for autoimmune hyperthyroidism
- Free T4 & TSH are useful for monitoring therapy in pregnancy

Auto-antibodies

Graves' disease (autoimmune thyroid disease) is the most common cause of thyrotoxicosis in women of childbearing age. Approximately 1% of pregnant women have been treated before, or are being treated during pregnancy for Graves' hyperthyroidism. Treatment will often render women euthyroid or hypothyroid.

Percentage of cases associated with positive autoantibodies for various conditions:			
	TSH receptor antibodies (TRAbs)	**Thyroid peroxidase antibodies (TPOAb)**	**Thyroglobulin antibodies (TgAb)**
Grave's Disease	90%	70%	50-70%
Hashimoto's Thyroiditis	10-15%	>90%	>80%
Thyroid Cancer	No association	Sporadic	25%
Other Conditions	15% multinodular goitre	>60% post-partum thyroiditis	40% in other autoimmune diseases (e.g. T1DM)
General Population	Negative	5%	5%

- Most TRAbs are stimulating (TSAbs) but can also be blocking (TBAbs), or neutral (N-TRAbs) depending on their effect on the TSH-receptor.
- Changes of functional properties from stimulating to blocking the TSH-receptor may occur during pregnancy.
- The typical clinical features of Graves' disease (goitre, hyperthyroidism, ophthalmopathy, dermopathy) occur when TSAbs (stimulating antibodies) predominate.
- As more thyroid hormone is produced, TgAb levels increase.

TRAbs easily cross the placenta from the first weeks of gestation. In most cases, the pregnancy-related immunosuppression reduces the levels of TRAbs during pregnancy. However, in women with active disease as well as in women who received definitive therapy (radioiodine or surgery) before pregnancy, they tend to persist.

KEY MESSAGE:

- **Women with a history of Graves' Disease, even if euthyroid or hypothyroid through radioiodine treatment or surgery, must have a TSH-receptor antibodies (TRAbs) measured early in pregnancy irrespective of the thyroid function test profile.**

Hyperemesis Gravidarum (HG) and Gestational Hyperthyroidism (GH)

Some pregnancies are associated with a mild transient physiological hyperthyroidism during the first half of pregnancy. This is caused by very high levels of ßhCG subunit that have a mild stimulatory effect on the thyroid. In approximately 3% of pregnancies the TSH will be suppressed to <0.01-0.02mU/L and FT4/FT3 may be slightly elevated.

It is essential to exclude Graves' disease in such pregnancies, and as such FT3 must be checked (normal in HG/GH), along with TSH-receptor antibodies (TRAbs) (absent in HG/GH).

An endocrine and/or obstetric opinion should be sought. Rehydration +- metoprolol is an option along with growth scans. If HG does not resolve and TFT shows depressed TSH and elevated FT4, treat with PTU under endocrinology guidance.

Obstetric Risks

- If hypothyroidism is well controlled pregnancy complications are unlikely. There is an increased risk of miscarriage, low birthweight, preterm birth, pre-eclampsia and stillbirth in women with untreated or suboptimal treated thyroid disease.
- Placental permeability is low early in pregnancy and increases progressively. The fetal thyroid becomes responsive to TSH, and to TRAbs at around week 20 of gestation.
- Fetal hyperthyroidism, which is the more common and expected dysfunction, develops usually at around 26 weeks, or as early as 18 weeks in severe cases.
- Transient neonatal hyperthyroidism occurs in less than 2% cases due to trans-placental passage of TSH receptor antibody (TRAb) which stimulates the fetal thyroid gland.

Obstetric Care

Antenatal Care

- All women with hyperthyroidism in pregnancy should be seen by a Consultant Endocrinologist and a Consultant Obstetrician from early in pregnancy.
- If the thyroid function testing remains stable, ongoing care can be shared with the community midwife and GP.
- Home delivery is not appropriate for women with hyperthyroidism.
- Commence serial ultrasound scans initially every 3-4 weeks or more frequent if poorly controlled TFT.
- Complete a neonatal referral.

Intrapartum and Postpartum Care

- Inform the paediatricians at the time admission to labour ward, and at the time of delivery.
- Many women will have stopped CBZ/PTU prior to delivery but if not take TSH/FT4/Total T3 on cord blood at delivery.
- The baby should have a resting heart rate checked and remain in hospital for at least 24 hours. Other congenital related problems are unlikely at doses of CBZ<15mg or PTU<150mg daily.
- Many women will not require to return to their CBZ/PTU post-natal but all should be seen in the Endocrine Clinic 8-12 weeks post-partum or sooner if they have symptoms.
- CBZ and PTU are safe in low dose for breast feeding (give in divided doses immediately after the feeds):
    - CBZ is safe at or below 15mg daily (max 30mg)
    - PTU is safe at or below 150mg daily (max 300mg)
- Ensure an endocrine clinic appointment is made for 6-8 weeks after delivery as there can be an exacerbation of thyrotoxicosis postnatally.

Monitoring

If the woman's serial thyroid testing remains stable, ongoing thyroid function testing is usually shared with the GP and supported by the community midwife.

Fetal Surveillance

Growth scans are 28, 32 and 36 weeks due to the risks associated with hypothyroidism. More scans may be required if the thyroid disease is poorly controlled.

Blood Testing During Pregnancy

TFTs, TRAbs and TPOAbs testing should be considered in women with suspected, past or established hyperthyroidism:

	When to Take Test	Plan
TFTs	Routine test for past or suspected thyroid disease and ongoing follow up	• Organise thyroid function test (TFT) at booking or at 6-8 weeks' gestation, then every 4-6 weeks until delivery, aiming to keep FT4 at upper limit of normal. • Repeat TFT 4 weeks after adjusting the dose of PTU. • Repeat TFT's 4-8 weeks after delivery and adjust levothyroxine dose accordingly (usu. to pre-pregnancy levels).
TRAbs	Suspected or known past Graves' disease	• TRAbs NEGATIVE (undetectable) **they do not need to be repeated**. • TRAbs POSITIVE further measurements of TRAbs will be required during pregnancy. o repeat at 18 to 22 weeks' gestation. As TRAb can cross the placenta and cause fetal hyperthyroidism and neonatal Graves' disease o **women with active Graves' disease or positive TRAb at 18 to 22 weeks' gestation should have monitoring for fetal hyperthyroidism by a maternal-fetal medicine specialist.**
TPOAbs	Suspected, known or past Graves' disease or elevated TSH	• If Graves' disease is suspected but not been previously diagnosed, TPOAb levels should be checked and would be expected to be elevated.

Drug Therapy

- Drug therapy is the treatment of choice for hyperthyroidism during pregnancy because antithyroid drugs also cross the placenta, and therefore decrease both the maternal and the fetal thyroid hormone production.
- There is no evidence that treating subclinical hyperthyroidism (normal FT4 and FT3 but TSH <0.02) improves pregnancy outcome. Treatment can potentially harm the fetus.
- Anti-thyroid therapy is ideally managed in conjunction with the endocrinologists.
- Propylthiouracil (PTU) is the drug of choice in the first trimester as there is a very slight risk of *aplasia cutis** with Carbimazole (CBZ). [Dose equivalent - Carbimazole 5mg = Propylthiouracil 50mg]
- (*Aplasia cutis is a congenital condition in which there is congenital absence of skin, with or without the absence of underlying structures such as bone. It most commonly affects the scalp, but any location of the body can be affected.)
- There is a small risk of serious liver dysfunction with PTU, consider changing to Carbimazole after 13 weeks'.
- Use the minimal dose of PTU or Carbimazole to maintain euthyroid status.
- Adjust dose of PTU only after consultation with the endocrinologists.

- For those with good control of thyrotoxicosis on doses of <15mg/day CBZ or <150mg/day PTU, the maternal and fetal outcome is usually good and unaffected by the thyrotoxicosis.

KEY MESSAGE:

- **Use PTU if LESS THAN 13 weeks**
- **Use CBX if MORE THAN 13 weeks**

(Dose equivalent - Carbimazole 5mg = Propylthiouracil 50mg)

OTHER CONSIDERATIONS

Other Thyroid Problems in Pregnancy

Thyroid Nodules and Thyroid cancer in Pregnancy

Thyroid nodules found during examination can be further assessed by ultrasound. Referral to an endocrinologist is needed for women with nodules detected during pregnancy.

If differentiated thyroid cancer (papillary or follicular thyroid cancer) is detected during pregnancy, surgery can be delayed until the postpartum period as such a delay is unlikely to affect the long-term prognosis.

Surgery in the second trimester may be considered for advanced differentiated thyroid cancer, medullary thyroid cancer or poorly differentiated thyroid cancer.

Post-Partum Thyroid Dysfunction

Postpartum thyroiditis affects 5 to 10% of women in the postpartum period, and is the most common cause of postpartum thyroid dysfunction. Women with a positive TPOAb. level have up to a 50% risk of developing postpartum thyroiditis, and those with a past history of postpartum thyroiditis have up to a 70% risk. Postpartum thyroiditis is typically associated with transient hyperthyroidism followed by transient hypothyroidism with eventual return to euthyroidism. Referral to endocrinology is indicated.

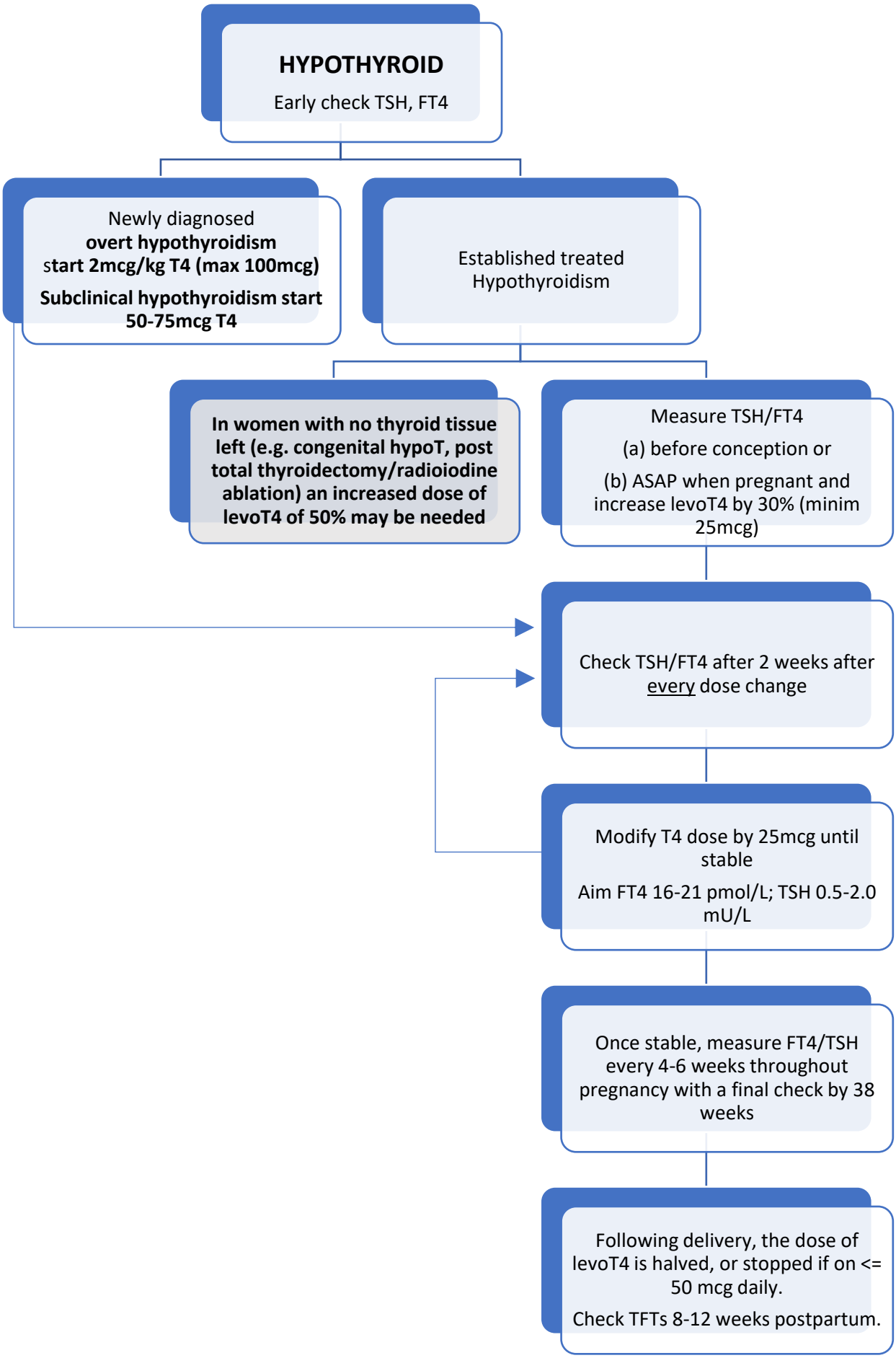
References

1. Wiles K. Management for women with subclinical hypothyroidism in pregnancy. *Drug and Therapeutics Bulletin* 2019;57:22-26.
2. Thillainadesan, S. Gargya, A. Thyroid disorders in pregnancy and postpartum. Endocrinology Today. 2019; 8(1): 8-12
3. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2017.
4. Alexander EK, Marqusee E, Lawrence J et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. NEJM 2004; 351:241-9.
5. Demer LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol 2003; 58:138-40.
6. Toft A. Increased levothyroxine requirements in pregnancy. Why, when and how much? NEJM 2014 ;351(3): 292-3.
7. Alexander EK, Pearce EN, Brent GA, *et al*. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid* 2017;27:315–89.
8. De Groot L, Abalovich M, Alexander EK, *et al*. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543–65.
9. Lazarus J, Brown RS, Daumerie C, *et al*. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 2014;3:76–94.

10. Bucci I, Giuliani C, Napolitano G. Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance.
11. World Health Organisation. Iodine supplementation in pregnant and lactating women. *e-Library of Evidence for Nutrition Actions (eLENA)*. 2020. URL: https://www.who.int/elena/titles/iodine_pregnancy/en/.
12. The Lancet "Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)". Vol. 382, Issue 9889, P331-337, July 27, 2013.

APPENDICES AND FLOWCHARTS

Flowchart on Management of Hypothyroidism in Pregnancy



Flowchart on Screening for Thyroid Disease in Pregnancy