RCOG Green-top Guideline (New)
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Management of Thyroid Disorders in Pregnancy

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Guideline

This is the first edition of this guideline.

Key Recommendations

- To diagnose thyroid dysfunction in pregnant women, trimester-, population-, and manufacturer- specific reference ranges for serum thyroid stimulating hormone (TSH) and free thyroxine (fT4) are recommended for correct interpretation of thyroid function tests. (Grade B)
- To achieve the recommended daily iodine intake of 200–250µg when planning pregnancy, and during pregnancy and breastfeeding, consideration should be given to increasing dietary intake of iodine-rich foods or consuming daily oral supplementation of 150µg iodine in the form of potassium iodide, as present in common prenatal supplements. (Grade C)
- Subpopulations with specific risk factors who are known to have a higher prevalence of overt thyroid disorders should be tested for thyroid dysfunction as soon as possible in pregnancy, preferably in the first trimester. (Grade D)
- In women with overt hypothyroidism (OH) and severe subclinical hypothyroidism (SCH; TSH >10 mU/L), titration of levothyroxine to achieve a preconception target TSH ≤2.5 mU/l is recommended. (Grade B)
- Women on levothyroxine therapy should be counselled to empirically increase their dose of levothyroxine by approximately 25–30% in the event of a positive pregnancy test. (Grade A)
- In women with overt hypothyroidism and severe SCH (TSH >10 mU/L), newly diagnosed at any time in pregnancy, commence levothyroxine treatment as soon as possible at a suggested dose of 1.6 micrograms per kg per day with repeat thyroid function tests in 4 weeks. (Grade B)
- In women with subclinical hypothyroidism (TSH between the upper limit of the reference range and 10 mU/L accompanied by normal fT4), newly diagnosed at any time in pregnancy, levothyroxine should be considered, at a suggested dose of 1.0–1.2 micrograms per kg per day. Otherwise perform thyroid function tests at 4–6 week intervals up to 20 weeks' gestation and at 28 weeks' gestation to check for development of OH or severe SCH, which would warrant treatment. (Grade B)
- For all pregnant women treated with levothyroxine, TSH and fT4 concentrations should be checked every 4–6 weeks until 20 weeks of gestation then once again at 28 weeks of gestation. (Grade A) Aim to keep the TSH below 2.5 mU/L while keeping the fT4 within the normal trimester-specific reference range. (Grade C)
- Routine testing for thyroid peroxidase antibodies (TPOAb) in euthyroid women is not recommended in pregnancy. (Grade B)
- If a woman is already known to be positive for TPOAb but euthyroid, they should be offered thyroid function test measurements in the first trimester (preferably at first contact with a

healthcare professional, including primary care booking) and at 20 weeks of pregnancy to detect development of hypothyroidism. (Grade C)

- Levothyroxine treatment is not recommended for women with TPOAb in the absence of thyroid dysfunction during pregnancy. (Grade A)
- Women with hyperthyroidism who are on antithyroid drugs while trying to conceive should be on propylthiouracil (PTU) in preference to carbimazole (CMZ), at the lowest effective dose to maintain fT4 concentrations in the upper half of the reference range. (Grade B)
- When pregnant, where a woman with a history of hyperthyroidism has been euthyroid (TSH in the reference range) for 6 months or more on a low dose of an antithyroid drug (Carbimazole [CMZ] <10 mg or Propylthiouracil [PTU] <200 mg daily), consider discontinuing antithyroid drugs with close thyroid function monitoring. (Grade D)
- If antithyroid drug treatment is required and the woman conceives on CMZ, a switch to PTU should be made before 10 weeks' gestation, with an advised dose ratio of 1:20 (CMZ:PTU). (Grade D)
- Women on antithyroid drugs should have thyroid function monitored every 2–4 weeks with measurement of serum TSH and fT4. Give consideration to fortnightly testing in the first half of pregnancy following the stopping of antithyroid drug treatment, when switching between antithyroid drugs, and following dose adjustments. (Grade D)
- Titration of antithyroid drugs should target fT4 concentrations in the upper half of the trimester-specific reference range. (Grade D)
- Serial ultrasound scans to assess fetal biometry with umbilical artery Doppler at monthly intervals from 26-28 weeks is recommended in those who at any time during pregnancy had uncontrolled Graves' disease, required antithyroid drug treatment or had a TSH-receptor antibody (TRAb) level three times above the threshold of positivity. (Grade D)
- TRAb measurement in the first trimester is recommended in all women with a history of Graves' disease, even following definitive treatment. If it is above the threshold of positivity or if the woman is on antithyroid drugs, a further measurement at 20 and 28 weeks of gestation is recommended to assess risk of fetal/neonatal Graves' disease. (Grade D)
- Neonates of women with known Graves' disease, of those receiving antithyroid medication during pregnancy and those with increased TRAb levels should have their thyroid function monitored soon after birth and at 1–2 weeks post-birth. (Grade D)
- Both CMZ and PTU are considered safe during breastfeeding and the lowest effective dose should be administered during the period of lactation with monitoring of the child's growth and development. (Grade C)
- Gestational transient thyrotoxicosis needs to be distinguished from Graves' disease/nodule-related hyperthyroidism using a range of clinical features. Gestational transient thyrotoxicosis, if accompanied by nausea and vomiting of pregnancy, requires supportive treatment only with no evidence that treatment with antithyroid drugs improves obstetric and fetal outcomes. (Grade C)
- In all women with new or enlarging clinically detectable thyroid nodules or goitre in pregnancy, check thyroid function and refer to an appropriate specialist for assessment to exclude malignancy and airway obstruction. Women with an enlarged thyroid in pregnancy should be reviewed by an obstetric anaesthetist. (Grade D)
- Routine testing for postpartum thyroiditis is not recommended. In women with risk factors for PPT who experience symptoms of thyrotoxicosis, thyroid function tests should be performed. (Grade D)

1. Purpose and scope

Thyroid disease is a common endocrine disorder in women and people of childbearing age. There is variation in clinical practice and approach to this globally, in part influenced by differences in population iodine status. There remains controversy regarding testing for and management of thyroid disorders before conception, during pregnancy and postpartum. This guideline presents the available evidence for best practice and, where evidence is lacking, consensus opinion by a multidisciplinary, cross-specialty team of authors is presented.

Preconception testing for thyroid dysfunction in the subfertile and recurrent miscarriage populations is not within the scope of this guideline and is addressed in a separate RCOG Scientific Impact Paper.[1]

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2. Introduction and background epidemiology

Dynamic changes occur in thyroid function through the course of pregnancy, to provide adequate concentrations of thyroid hormone to the woman and fetus.[2-4] Overall, demands on maternal thyroid hormone production increase by approximately 50% during pregnancy; this requires both an adequate supply of iodine for the biosynthesis of thyroid hormones and the absence of significant thyroid disease.

Increased estrogen in pregnancy raises thyroxine-binding globulin (TBG) concentrations, starting very early in pregnancy, and plateauing by approximately 18–20 weeks of gestation. To maintain adequate free thyroid hormone concentrations, thyroxine (T4) and tri-iodothyronine (T3) production by the thyroid gland increases during the first half of pregnancy, a new steady-state is reached by mid-gestation and the synthesis of thyroid hormones returns to pre-pregnancy rates. First trimester increases in human chorionic gonadotrophin (hCG), which has weak thyroid-stimulating activity, transiently increases free thyroxine (fT4) and free tri-iodothyronine (fT3) and decrease thyroid stimulating hormone (TSH).[5] From mid-gestation, as hCG declines, serum fT4 and fT3 concentrations decline gradually, while serum TSH concentrations rise slightly.

Iodine requirement increases considerably during pregnancy as there is increased consumption of iodine for thyroid hormone synthesis and increased renal iodine clearance.[6] The placenta may also be an organ of storage for iodine.[7] The fetal thyroid begins to take up iodine from 10–12 weeks of gestation and begins to release appreciable amounts of thyroid hormone from 18–22 weeks' gestation. Breast milk production from the second half of gestation adds further to maternal iodine demand.[8]

Maternal thyroid hormones are essential for the maintenance of pregnancy and may influence placental development.[9] Transplacental passage of maternal T4 is essential for normal fetal development, especially neurodevelopment during the first half of gestation.[10-12] The fetus is completely dependent upon maternal T4 prior to commencing production of its own thyroid hormone but remains reliant on maternal supply of iodine[2] and continues to receive maternal T4 until birth.[13]

Table 1: Common thyroid function disorders in pregnancy

Condition	Definition by thyroid function testing		Reported prevalence in pregnancies[a]
	TSH concentration	fT4 concentration	
Overt hypothyroidism (OH)	Increased	Decreased	0.2–1% (including undiagnosed, partially-treated and adequately-treated hypothyroidism)
Subclinical hypothyroidism (SCH)	Increased	Normal	2.2–10%
Isolated hypothyroxinaemia (IH)	Normal	Decreased	1.3–8%
Thyrotoxicosis[b] (including gestational transient thyrotoxicosis)	Decreased	Increased	1–5%
Overt hyperthyroidism[b] (Graves' disease and toxic nodular hyperthyroidism)	Decreased	Increased	0.05–1.3%
Subclinical hyperthyroidism	Decreased	Normal	1.5–2.0%

[a]Using trimester-specific reference ranges in iodine replete and mild-moderately iodine deficient populations. Excludes populations with severe iodine deficiency.

[b]Hyperthyroidism is the increased production and secretion of thyroid hormones whereas thyrotoxicosis refers to the clinical symptoms and signs of excess circulating thyroid hormones, which may not be due to excess thyroid hormone production or hyperthyroidism. Hence, hyperthyroidism comprises a subset of thyrotoxic cases.

Abbreviations: TSH, thyroid stimulating hormone; fT4, free thyroxine

Worldwide, iodine deficiency is the leading cause of preventable neurodevelopmental defects.[14] Among populations of severe iodine deficiency (defined by a median urinary iodine concentration in a population of <20microgram/L) there is increased risks of endemic goitre, hypothyroidism, neurological and developmental impairment, subfertility, miscarriage, infant mortality, trophoblastic or embryonic fetal disorders, profound intellectual impairment, deaf-mutism and motor rigidity in children, and childhood and adult learning difficulties.[15] In these areas of severe iodine deficiency, thyroid nodules have been reported in up to 30% of pregnant women and people.[16] In regions of mild to moderate iodine deficiency pregnant women are also at increased risk for the development of goitre[17] and thyroid disorders,[18] with one observational study reporting an association with small-for-gestational age and preterm birth[19] but others showed no association with any adverse obstetric outcome.[20] However, associations between maternal urinary iodine concentrations (UICs), and altered executive function,[21] attention deficit and hyperactivity disorders in children[22] and impaired cognitive outcomes[21,23,24] have been reported. Meanwhile, in areas with adequate dietary iodine intake, variations in maternal UICs have been shown to have limited influence on neonatal and infant developmental outcomes.

In iodine-replete and mildly iodine deficient populations, autoimmunity is the commonest aetiology for thyroid disorders. Untreated and inadequately-treated overt hypothyroidism (OH) is associated with an increased risk of spontaneous miscarriage, perinatal death, pre-eclampsia, pregnancy-induced hypertension, preterm birth, low birth weight and postpartum haemorrhage.[25-27] Untreated overt hyperthyroidism, commonly due to Graves' disease, is also associated with increased risks, in particular pre-eclampsia, preterm birth, fetal growth restriction and maternal heart failure.[28-30]

Gestational transient thyrotoxicosis is common, affecting 1–5% of pregnancies in Europe,[28] and is usually benign and self-limiting. Hyperthyroidism in pregnancy is rarer and usually caused by Graves' disease; prevalence in pregnancy: 0.5–1.3% pre-existing Graves', 0.05% new onset Graves', 0.1% toxic

nodular disease.[4,29] Autoimmune Graves' disease is mediated by the presence of stimulating TSH-receptor antibody (TRAb), and commonly improves with advancing gestation. Thyrotoxicosis is not always associated with hyperthyroidism. Thyrotoxicosis usually does not need treatment, but hyperthyroidism requires active intervention. Subclinical hyperthyroidism is defined as below normal serum TSH concentrations with normal concentrations of circulating thyroid hormones. Current evidence indicates that it is not associated with adverse fetal or pregnancy outcomes and therefore, does not require treatment (See Appendix 4).[31,32]

Thyroid autoimmunity (TAI) is the presence of circulating antithyroid autoantibodies that are targeted against the thyroid, with or without thyroid dysfunction. Thyroid peroxidase antibodies (TPOAb) are the most common antithyroid autoantibody, present in approximately 10% of women.[33] Euthyroid TAI has been associated with increased risk of miscarriage, preterm birth and postpartum thyroiditis.[34,35] When looking at TAI in conjunction with thyroid dysfunction, there may additionally be an association with increased risks of pre-eclampsia and gestational diabetes.[36-38]

The incidence of clinically apparent nodules or goitre presenting in pregnancy in iodine-replete and mildly iodine-deficient areas is low.[39] Ultrasound-detected nodules are more common with increasing parity and age.[40,41] When a new thyroid nodule or goitre is diagnosed in pregnancy, local symptoms such as tracheal compression should be assessed, and malignancy and hyperthyroidism excluded.

There is controversy concerning the need and cost-effectiveness of routinely testing for thyroid disease and for TAI in the first trimester of pregnancy or in women who are planning for pregnancy. Whether levothyroxine treatment improves pregnancy and offspring outcomes in subclinical hypothyroidism (SCH) and isolated hypothyroxinaemia (IH) remains debatable. Controversies in the care of these conditions for the general obstetric population will be discussed in this guideline. Uncertainties in the management of thyroid function abnormalities in the care of subfertility and recurrent miscarriage is addressed specifically in a separate RCOG Scientific Impact Paper.[42]

Both inadequate and excessive treatment of thyroid disorders, the choice of treatment, as well as delayed commencement and adjustment of treatment, can also result in detrimental effects on the pregnancy and fetus. Therefore, care should be optimised prior to conception, during pregnancy and after birth, and should be provided by clinicians with appropriate experience. There should be a clear designated primary clinician and this will depend upon local expertise. This is important to ensure continuity of care over the course of pregnancy, minimise confusion with regards treatment adjustments and to improve overall experience. Where possible, pregnant women and people with thyroid disorders should be seen in joint multidisciplinary clinics comprising clinicians with obstetric and endocrine expertise.

3. Identification and assessment of evidence

This guideline was developed using standard methodology for developing RCOG Green-top Guidelines (GTGs).[43] The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects [DARE] and the Cochrane Central Register of Controlled Trials [CENTRAL]), EMBASE, MEDLINE and Trip were searched for relevant papers. The search was inclusive of all relevant articles published until March 2022. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search. Search terms included '*thyroid diseases', '*euthyroid sick syndromes', '*goiter', '*hyperthyroidism', '*hyperthyroxinemia', '*thyroid dysgenesis', '*thyroid nodule'and '*thyroiditis'. The search was limited to studies on humans and papers in the English language. Relevant guidelines were also searched for using the same criteria in the National Guideline Clearinghouse and the National Institute for Health and Care Excellence (NICE) Evidence Search.

Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and graded accordingly. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix 1.

4. Thyroid function tests in pregnancy

4.1 What are the reference ranges for thyroid function tests in each trimester?

Recommendation	Evidence quality	Strength	Rationale for recommendation
To diagnose thyroid dysfunction in pregnant women, trimester-, population-, and manufacturer-specific reference ranges for serum TSH and fT4 are recommended for correct interpretation of thyroid function tests.	**2+**	**B**	Thyroid function changes significantly with gestational age. There is significant variation in the manufacturers' assays used to measure TSH and fT4.
Where your laboratory does not provide such reference ranges those in Appendix 2 may be used for guidance. In the absence of appropriate information it is reasonable to set an upper limit for TSH of 4.0 mU/L in pregnancy.	**3**	**C**	A TSH of 4.0 mU/L approximates with the upper limit of the first trimester reference range for most assays, and many studies use this threshold in reporting associations with risk of pregnancy complications.
For pregnant women who are on any thyroid-related medication, more specific treatment targets for TSH and fT4 are recommended (see sections 7–9).	**2+**	**C**	Use of treatment targets for TSH and fT4 are associated with improved pregnancy outcomes.

Due to pregnancy-induced changes in thyroid function, use of reference ranges derived from non-pregnant individuals are not applicable[44] and carry the risk of misdiagnosis.[45,46] *[Evidence level 2+]*

Furthermore, the physiological changes that occur in normal pregnancy affect measurement of fT4 using immunoassay in a variable way, depending on the manufacturer's method being used. To overcome these issues it is recommended that trimester-specific, population-specific and method-manufacturer-specific reference ranges are used.[46,47] *[Evidence level 2+]*

If such reference ranges are not routinely provided alongside thyroid function test results, the laboratory should inform clinicians when there are changes in assays used for thyroid function testing and advise on appropriate pregnancy related reference ranges.

In conditions where hCG may be higher such as multiple pregnancies, TSH concentrations are correspondingly lower.[48] *[Evidence level 2+]*

5. Iodine and supplementation in pregnancy

5.1 What is the recommended total daily iodine intake in women in the UK who are planning pregnancy, who are pregnant and who are breastfeeding?

Recommendation	Evidence quality	Strength	Rationale for recommendation
All pregnant and breastfeeding women should have a total daily intake of approximately 200–250 microgram iodine.	**1+**	**B**	To avoid iodine deficiency in pregnant and lactating women and in the fetus/newborn.
To achieve the recommended daily iodine intake when planning pregnancy, and during pregnancy and breastfeeding, consideration should be given to increasing dietary intake of iodine-rich foods or consuming daily oral supplementation of 150 microgram iodine in the form of potassium iodide (as present in common prenatal supplements).	**2–**	**C**	To avoid iodine deficiency at the time of conception, and during pregnancy and breastfeeding.
If deemed appropriate, supplementation should ideally be started three months in advance of pregnancy or as soon as possible in pregnancy.	**4**	**GPP**	Iodine status and thyroid function should be optimal at the point of conception to avoid iodine deficiency in pregnancy.
Women should take a single rather than multiple iodine-containing supplements at the same time.	**4**	**GPP**	To avoid excess iodine intake.
Sustained iodine intake from diet and dietary supplements exceeding 500 microgram daily should be avoided during pregnancy.	**2+**	**C**	Excess iodine intake could potentially lead to development of fetal and maternal thyroid dysfunction.
Individual assessment of iodine status in pregnancy and in women planning pregnancy is not recommended.	**2++**	**B**	Single spot or 24-hour urinary iodine quantification and thyroid function tests are not valid markers for the iodine nutritional status of individual women.

Iodine requirements vary depending on age and physiological status,[49] with pregnant and lactating women having the highest requirements. *[Evidence level 2++]*

There is international consensus about the required total iodine intake being 200–250 microgram iodine daily. However, different organisations have made slightly different recommendations on how the increased iodine needs could be met.[14,50-52] An important distinction needs to be made between total iodine ingested and the dietary supplementation that may be required to achieve the total daily iodine intake.

Iodine content is low in most naturally occurring foods[53] and for most people across the world, the chief source of dietary iodine is added iodine, either from salt-fortification or from dairy products where iodine is added to animal feed or because of the use of iodine-containing antiseptics. Important sources of iodine in the diet include cow's milk (non-organic milk 50–100 microgram per 200ml) and yoghurt (50–100 microgram per 150gm), and the iodine content of fish such as cod (~70 microgram per 100g) and haddock (~430 microgram per 100g) is high. In general, marine fish (average ~20microgram per 100g) have a higher iodine content than freshwater fish (average ~6.5microgram per 100g).[54] Given the concern of mercury contamination, pregnant women should not consume more than 2–3 servings of fish a week. Individuals who have a low intake of foods with higher iodine content (e.g. dairy products, fish and iodised salt) could be considered at risk of having low iodine intake, and iodine supplementation should be recommended. Food factsheets for women in the UK are available.[55] However, excessive intake of highly iodine-rich foods should be avoided.

Median urinary iodine concentrations (UICs) are markers of population iodine status. Urinary iodine testing is not beneficial for individual assessment since there is substantial diurnal and day-to-day variation in urinary iodine excretion and, therefore, UICs cannot be used to identify particular individuals with iodine deficiency.[56,57] *[Evidence level 2++]*

Surveys of urinary iodine in some geographical areas around the world continue to reveal significant numbers of young women with suboptimal iodine nutrition, particularly during pregnancy and lactation, even in areas where iodisation of salt has been implemented.[58-60] *[Evidence level 2+]*

There is currently controversy about whether women of reproductive years in the UK are deficient in iodine. A previous nationwide UK study of 14–15-year-old girls in 2009 found mild iodine deficiency[61] but the National Diet and Nutrition Survey (NDNS)[62] found, on average, adequate iodine status in women of childbearing age (16–49 years of age) and children (aged 4–18 years of age) by 2016. A more recent study[63] of urinary iodine concentrations in pregnancy in three UK cities demonstrated iodine concentrations were insufficient in the second and third trimesters of pregnancy. Currently in UK, there is an absence of conclusive evidence regarding sufficiency of iodine intake by women in the reproductive years and there is evidence that at least 50% of women are iodine deficient in the first trimester of pregnancy. In addition, studies have shown that knowledge of iodine requirements and sources is very poor among pregnant women in the UK.[63]

The timing of supplementation is likely to be important. If iodine supplementation is commenced pre-pregnancy in iodine-deficient populations, improved maternal thyroid function can be observed, depending on dose and the timing of initiation; beneficial effects of iodine on fetal development are likely to be greater with commencement of supplementation at an earlier gestation.[64] *[Evidence level 3]*

While there is strong evidence that correction of severe iodine deficiency at a population level will reduce intellectual impairment in children,[65,66] studies investigating the benefits of individual iodine supplementation in pregnancy in populations of mild-moderate iodine-deficiency have shown inconsistent results.[67-72]

A 2017 Cochrane meta-analysis included over 2700 women, mostly from populations of mild to moderate iodine deficiency.[73] Iodine supplementation decreased the likelihood of postpartum hyperthyroidism and increased the likelihood of gastrointestinal symptoms in pregnancy. There were no clear differences between groups for prevalence of hyperthyroidism in pregnancy, hypothyroidism or maternal TPOAb positivity in pregnancy or postpartum, or preterm birth. Iodine supplementation was associated with a non-significant trend of a lower perinatal mortality, with all of the observed

perinatal deaths occurring in one trial conducted in a severely iodine deficient setting. There were no clear differences in neonatal outcomes. *[Evidence level 2–]*

A study of daily iodine supplementation commencing in the early second trimester in pregnant women from a mild to moderately iodine deficient population demonstrated small negative effects on maternal T4 concentrations, but no effects on child development.[74] *[Evidence level 1–]* The median urinary iodine concentration in the placebo group in this study remained within the recommended range in the second and third trimesters, which may have been caused by a physiological increase in renal iodine clearance, or the recruited women may have had adequate iodine exposure before pregnancy, or because women enrolled in the study were told about the importance of iodine in pregnancy and may have increased their iodine intake.[75]

There were insufficient data to reach any meaningful conclusions on the benefits and harms of routine iodine supplementation in women before, during or after pregnancy. Because of study design limitations and wide confidence intervals, and due to the small number of trials included, these findings must be interpreted with caution. Almost all the evidence came from settings with mild to moderate iodine deficiency and therefore may not be applicable to settings with severe deficiency but may be applicable to the UK population. Modelling has suggested that universal iodine supplementation in pregnancy could be cost-effective,[8,76] but this is not yet practised in the UK.

Excess iodine exposure in pregnancy at sustained levels exceeding 500 microgram daily can cause serious adverse health effects for both the women and fetus, and should be avoided. This may occur through ingestion of supplements, water or foods with high iodine content, or because of medical treatments or procedures. Acute iodine poisoning may cause gastrointestinal or cardiovascular symptoms and coma,[77] and tends to occur in iodine replete areas. It is unlikely that oral iodine supplementation in doses present in common prenatal supplements during pregnancy and breastfeeding for UK woman will lead to iodine levels that will cause such adverse health effects in women and their babies. *[Evidence level 3]*

Women with diagnosed and treated overt thyroid disorders may safely consume common prenatal supplements containing iodine (approximately 150 mcg daily). *[Evidence level 4]*

6. Testing for thyroid disease during pregnancy

6.1 Should all pregnant women be tested for thyroid dysfunction at pregnancy booking?

Recommendation	Evidence quality	Strength	Rationale for recommendation
Universal testing for thyroid dysfunction during pregnancy is not recommended.	**2+**	**C**	Current available evidence shows no improvement in overall population pregnancy outcomes with universal testing.

Proponents of universal testing have argued that a case for testing for overt hypothyroidism (OH) can be made since it is a prevalent condition (0.2–1% of pregnancies)[78-87] that has serious consequences if untreated (adverse pregnancy and neurodevelopmental effects), it can be asymptomatic in approximately 70%,[88] it is safely detectable by a thyroid function test, and can be treated with levothyroxine to avert adverse consequences. However, the overall cost-effectiveness remains debatable. If a universal aproach for thyroid function testing is adopted, OH will only constitute a small proportion of abnormal results with the vast majority falling into the gestational transient

thyrotoxicosis, subclinical hypothyroidism (SCH) and isolated hypothyroxinaemia (IH) groups, where the benefit of treatment is not yet proven.

The Controlled Antenatal Thyroid Screening (CATS) study in UK and Italy was a prospective RCT investigating the benefit of pregnant population screening (n = 21 846) for an increased TSH concentration (SCH or hypothyroidism) or a low fT4 concentration (isolated hypothyroxinaemia [IH]) for improving neurocognitive outcomes of children.[89] In total 5% screened positive, of which 390 were in the intervention group who initiated levothyroxine 150 micrograms per day at a mean of 13^{+3} weeks of gestation, and 404 were in the control untreated group. This study demonstrated no difference between groups in child cognitive function at 3 years of age.

Another study in the US screened 97 228 pregnant women between 8–20 weeks of gestation and found 6.8% of results abnormal, consisting of 0.5% with OH, 0.3% overt hyperthyroidism, 3% SCH and 3% IH. Women with SCH (n = 677) and IH (n = 526) were randomised in a placebo-controlled trial which showed no significant effect of levothyroxine therapy, when commenced at a median gestation of 17 weeks, on child cognitive function and other indexes of neurodevelopment up to 5 years of age, as well as on adverse pregnancy and neonatal outcomes.[90] *[Evidence level 1–]*

6.2 Should thyroid function testing be carried out in a targeted population of pregnant women who are at risk of thyroid dysfunction?

Recommendation	Evidence quality	Strength	Rationale for recommendation
Subpopulations with specific risk factors who are known to have a higher prevalence of overt thyroid disorders should be tested for thyroid dysfunction as soon as possible in pregnancy (preferably in the first trimester).	**2–**	**D**	A risk-based approach to thyroid function testing during pregnancy remains controversial as there is a lack of global consensus on the factors which should trigger such testing. However, there are some well-established risk factors, and early identification and treatment of overt thyroid disorders improves pregnancy outcomes, therefore a risk-based approach is justified.
Risk-based testing in pregnancy should be for TSH and fT4 simultaneously.	**4**	**GPP**	This avoids any additional delays in making a diagnosis and facilitates starting treatment in the first trimester where possible.

Since untreated overt thyroid dysfunction is associated with poorer pregnancy and child outcomes, it is reasonable to consider targeted testing strategies based on existing observational data until new information comes to light. However, testing is more likely to uncover subclinical thyroid conditions. Subclinical thyroid dysfunction in obstetric populations is typically not the dominant factor dictating obstetric and childhood outcomes, but could add significantly to the risk imposed by co-morbidities. Treatment efficacy and cost effectiveness is likely not equivalent in women of low and high obstetric risk, although no such comparative study has been conducted.

Targeted testing as soon as possible in pregnancy, preferably by the middle of the first trimester, should be offered to women at an increased risk of thyroid dysfunction (Table 2). Consideration for

testing should be given to three broad groups of women: those with a personal history of a thyroid disorder or at risk of progressive thyroid dysfunction in pregnancy; those with autoimmune conditions who are at risk of hypothyroidism and obstetric complications; and those with a history of late miscarriage or stillbirth.

Women with a personal history of a thyroid disorder or at risk of progressive thyroid dysfunction in pregnancy

These include those with a history of a thyroid disorder (previous thyroiditis, subclinical hypo- or hyperthyroidism, thyroid nodule, known TPOAb positivity) or thyroid insult (for example, a history of thyroid surgery, radioiodine ablation, previous head/neck irradiation), women on thyroid disruptive medication (such as amiodarone, lithium) or with typical discriminatory signs and symptoms of a thyroid disorder (for example, a goitre, cardiac dysrhythmias). It has been shown that at 8 years post head or neck irradiation, 67% of women developed hypothyroidism.[91] After post-partum thyroiditis, 10% remain permanently hypothyroid while approximately 20–30% become hypothyroid in 3–5 years and 50–60% by 8–10 years post-birth.[92-96] One later study even reported a rate of permanent hypothyroidism as high as 54% at the end of the first postpartum year. Study differences are likely due to differences in population iodine status and participant characteristics, and study methodology. *[Evidence level 2++]*

In cases of thyroid autoimmunity (TAI) and previous thyroid damage, in addition to the established risk of progression when not pregnant, the risk of development of hypothyroidism further increases in pregnancy.[97,98]

Women with autoimmune conditions who are at risk of hypothyroidism and obstetric complications

Autoimmune disorders in general are associated with a higher prevalence of hypothyroidism and hyperthyroidism. It is especially important to diagnose overt thyroid diseases in women known to have an autoimmune disorder that already puts them at a higher risk of pregnancy complications. The incidence of newly diagnosed OH in pregnancy in type 1 diabetes and systemic lupus erythematosus (SLE) have been reported to be 16%[99] and 11%,[100] respectively. Importantly, preterm birth occurred in 18% of euthyroid women with SLE compared with 65% if the woman had SLE with thyroid dysfunction detected at any time in pregnancy or postpartum,[100] suggesting a synergistic effect of thyroid dysfunction and SLE on pregnancy risk. Also the risk of congenital heart block in cases of maternal positivity for anti-Ro or anti-La was also higher if the woman had concurrent thyroid dysfunction.[101] *[Evidence level 3]*

Women with a history of late miscarriage or stillbirth

Observational studies have linked overt and subclinical thyroid dysfunction with late pregnancy loss.[102,103] *[Evidence level 2–]*

In line with RCOG Green-top Guideline No. 55 *Late Intrauterine Fetal Death and Stillbirth*,[104] which recommends thyroid function testing as part of the immediate post-partum investigation for stillbirth, thyroid function testing should be considered in women with a previous history of stillbirth or second trimester miscarriage when planning conception or at booking of subsequent pregnancies if they had not previously had a normal thyroid function test post-adverse event.

Table 2: Conditions and risk factors which should trigger thyroid function testing in early pregnancy

Personal history of a thyroid condition or previous insult	Autoimmune conditions associated with obstetric complication	Previous late pregnancy loss
Surgical/Structural o Previous thyroid surgery o Goitre o Thyroid nodule **Autoimmune/infection** o Previous overt or subclinical thyroid dysfunction o Previous thyroiditis (autoimmune or infectious or postpartum) o Known TPOAb positivity **Medical** o Previous radioiodine ablation o Recent/current thyroid disruptive medication (e.g. amiodarone, lithium) o Previous head/neck irradiation **Discriminatory signs and symptoms** o Cardiac dysrhythmia o Significant preconception weight loss o Enlarging thyroid gland	o Type 1 diabetes mellitus o Systemic Lupus Erythematosus o Anti-Ro/Anti-La positivity o Anti-phospholipid syndrome	o Stillbirth o Second trimester miscarriage **testing recommended if not previously tested at the time of pregnancy loss or post-adverse event*

7. Hypothyroidism

Retrospective observational studies of presumed treated overt hypothyroidism (OH) have shown no difference in pregnancy outcome compared with women without OH. However, the adequacy of OH treatment or the absence of hypothyroidism in the control group was not specifically ascertained.[105] Treatment needs to be adequate, and ideally optimised pre-conception, with appropriate advice given before pregnancy to prevent hypothyroidism in early pregnancy. Adverse pregnancy outcomes including premature birth, low birth weight, pregnancy loss, and impaired neurological development in babies are more common and severe in OH than in subclinical hypothyroidism (SCH). A retrospective study of more than 1000 pregnant women on levothyroxine replacement therapy, demonstrated that the risk of pregnancy loss increased proportionally to the degree of TSH elevation in the first trimester.[106] Similarly, the incidence of neurodevelopmental defects and lowering of children's IQ at 7–9 years of age demonstrated a graded response with higher maternal TSH concentrations during pregnancy associated with higher risk to children.[107] *[Evidence level 2+]*

The goal of levothyroxine treatment is to normalise and maintain maternal serum TSH values within the trimester-specific pregnancy reference range, and to mimic physiological changes and prospectively prevent abnormalities in thyroid function. Hence, dose titration using the lower half of the TSH reference range as a guide is commonly adopted during pregnancy (i.e. 0.1–2.5mU/L).[108] *[Evidence level 2–]*

In pregnancy, SCH may be defined as an increased TSH above the upper limit of the trimester-specific reference range, with severe SCH defined as cases with TSH greater than 10mU/L, accompanied by normal concentrations of thyroid hormones. The annual rate of progression of SCH to OH in the non-pregnant population ranges from 2–6%.[109] Risk factors for progression include increased TPO antibodies (TPOAb) and an initial TSH>10mU/L.[110] In pregnant women who are TPOAb positive, post-hemithyroidectomy, or treated with radioactive iodine, progression to OH is more likely due to the inability of the thyroid to augment production when needed during pregnancy. *[Evidence level 2+]*

Observational studies have linked SCH with adverse pregnancy outcomes. Meta-analyses of individual participant data (n = 47 045, 19 cohorts) showed that SCH was associated with a higher risk of pre-eclampsia (OR 1.53; CI 1.09–2.15),[111] preterm birth (OR 1.29; CI 1.01-1.64),[112] and small for gestational age at birth (OR 1.24; CI 1.04-1.48).[113] *[Evidence level 2+]*

Other meta-analyses reported increased risks of pregnancy loss (OR 1.93; CI 1.40–2.64); breech presentation at term (OR 2.3; CI 1.50–3.51); placental abruption (OR 2.16; CI 1.15–4.06);[114] and an increased incidence of neurodevelopmental defects (correlated with degree of TSH elevation).[107] *[Evidence level 2–]*

Levothyroxine treatment is recommended for pregnant women with severe SCH (TSH>10mU/L) where there is risk of further progression to overt hypothyroidism. Levothyroxine treatment should also be considered for those with SCH where the TSH is between the upper limit of the reference range and 10mU/L, particularly if TPOAb positive, in order to reduce the risk of developing overt hypothyroidism and associated complications in pregnancy.[51,115] Even though the two largest trials of treatment of SCH[89,90] (discussed in Section 6) reported no difference in maternal and child outcomes with levothyroxine treatment, they were still limited statistically by both sample size and late commencement of treatment, usually from the second trimester of pregnancy. When these trials were considered together with others in a systematic review and meta-analysis totalling 7 RCTs and 6 observational studies (N=7342)[116] it was concluded that levothyroxine treatment of SCH may reduce the risk of pregnancy loss (RR 0.79; CI 0.67-0.93) and neonatal death (RR 0.35; CI 0.17–0.72). *[Evidence level 2–]*

Another meta-analysis included only studies which defined SCH in pregnancy using a TSH threshold of greater than 4 mU/L; this study which included 3 RCTs and 3 observational studies (N=7955)[117] reported a reduction in pregnancy loss (OR 0.55; CI 0.43–0.7), as well as preterm birth (OR 0.63; CI 0.41–0.98) and gestational hypertension (OR 0.78; CI 0.63–0.97). *[Evidence level 2–]*

Isolated hypothyroxinaemia (IH) is considered to be a distinct biochemical entity, usually defined as an fT4 concentration below the 2.5th percentile, with a TSH within the reference range. However, there remains some variability of IH definition, and an absence of established regional reference ranges (that account for iodine status) in TPOAb negative populations could lead to misclassification of IH status.[118] The most common cause of IH is iodine deficiency.[82] Other proposed causes include obesity,[119] iron deficiency,[120] and exposure to organochlorine pesticides.[121]

Some studies have shown an association between hypothyroxinaemia and poorer cognitive development of the children.[122-124] Results from observational studies of IH on pregnancy outcomes are conflicting and a meta-analysis identified placental abruption alone to be increased in women with IH (pooled odds ratio 2.3 [95% CI 1.1–4.8])[114,125] but a causal link has not been established. *[Evidence level 2–]*

Existing randomised trials of women with SCH and IH diagnosed in pregnancy, with levothyroxine treatment mostly commenced in the second trimester of pregnancy, did not show improvement in child neurodevelopmental outcomes,[89,90] however, they were underpowered to assess efficacy within the subgroup of women who commenced levothyroxine in the first trimester of pregnancy (less than 12 weeks of gestation). The potential consequences of levothyroxine overtreatment should also be considered (see below).

Transplacental delivery of specifically maternal T4 is essential for the developing fetal brain from early first trimester of pregnancy.[12,123] The recommended treatment of maternal hypothyroidism is oral levothyroxine. It is strongly recommended that other thyroid preparations that contain non-T4 forms

of thyroid hormone, such as desiccated thyroid or combined levothyroxine and liothyronine therapy are not used in pregnancy, as these may result in insufficient transfer of maternal T4 to the fetal brain. *[Evidence level 3]*

7.1 How should women with hypothyroidism and SCH be cared for before pregnancy?

Recommendation	Evidence quality	Strength	Rationale for recommendation
In women with OH and severe SCH (TSH >10 mU/L), titration of levothyroxine to achieve a preconception target TSH ≤2.5 mU/l is recommended.	**2+**	**B**	TSH>10mU/L is a risk factor for progression to OH. A preconception TSH target ≤2.5mU/L is associated with a lower risk of hypothyroidism in the first trimester of pregnancy.
In women with SCH, particularly those already known to be TPOAb positive, treatment with levothyroxine should be considered starting preconception, with titration to achieve a preconception target TSH ≤2.5 mU/l.	**2–**	**C**	To reduce the risk of overt hypothyroidism and associated complications in pregnancy.
Women with an isolated low fT4 concentration (with normal TSH) diagnosed outside of pregnancy, should be referred to the Endocrinology team for further investigation.	**2–**	**C**	To evaluate for possible secondary hypothyroidism and exclude pituitary pathology.
Women on levothyroxine therapy should be counselled to empirically increase their dose of levothyroxine by approximately 25–30% in the event of a positive pregnancy test. This may be achieved by either: **– doubling the dose of levothyroxine on two days of each week or** **– implementing a dose increment of:** **• 25 micrograms per day for women taking 100 micrograms or less levothyroxine daily** **• 50 micrograms per day for women taking greater than 100 micrograms levothyroxine daily.**	**1+**	**A**	This reduces the risk of developing hypothyroidism in the first trimester as increased requirement for exogenous levothyroxine occurs as early as 4–6 weeks of gestation. Dose increments based on baseline levothyroxine dose or doubling the levothyroxine dose on two days of the week are equally valid.

In women with known OH and SCH, a preconception target TSH ≤2.5 mU/l is recommended as it may offer some protection against the development of hypothyroidism in early pregnancy.[126,127] When pregnant, the required levothyroxine dose increment may vary from 25 to 50%, depending upon the aetiology of hypothyroidism and pre-pregnancy TSH value. Given the median gestation of requiring a dose increase in pregnancy is around 5 weeks' gestation,[128] a self-initiated empirical dose increase by approximately 25–30% as soon as there is a positive pregnancy test can significantly reduce the risk of developing hypothyroidism in pregnancy, without any adverse consequences on the pregnancy, provided regular thyroid function monitoring in pregnancy is instituted.[129,130] *[Evidence level 1+]*

7.2 How should newly diagnosed hypothyroidism, SCH and IH be treated in pregnancy? (refer to summary in Appendix 3)

Recommendation	Evidence quality	Strength	Rationale for recommendation
In women with overt hypothyroidism and severe SCH (TSH >10 mU/L), newly diagnosed at any time in pregnancy, commence levothyroxine treatment as soon as possible at a suggested dose of 1.6 micrograms per kg per day with repeat thyroid function tests in 4 weeks.	**2++**	**B**	For timely achievement of target TSH.
In women with SCH (TSH between the upper limit of the reference range and 10 mU/L), newly diagnosed at any time in pregnancy, levothyroxine should be considered, at a suggested dose of 1.0–1.2 micrograms per kg per day. Otherwise perform thyroid function tests at 4–6 week intervals up to 20 weeks' gestation and at 28 weeks' gestation.	**2+**	**C**	Possible benefit may be greater if starting treatment as soon as possible in the first trimester, particularly if already known to be TPOAb positive. The recommended levothyroxine dose could achieve the target TSH safely. If not treated there is risk of disease progression especially given the increased thyroid demands of pregnancy, and close monitoring in pregnancy is then essential to detect development of overt hypothyroidism which would warrant treatment.
In women with IH (fT4 concentration below the 2.5th percentile, with normal TSH), routine levothyroxine therapy is not recommended. Thyroid function tests should be rechecked 4–6 weeks later to ensure it remains stable.	**2–**	**C**	There is no evidence of improved pregnancy and child outcomes with levothyroxine treatment. Surveillance alone to ensure stability is appropriate in the majority of cases.

Thyroxine dosing strategies may be based on body weight, TSH values or utilisation of a standard starting dose. When OH is newly diagnosed during pregnancy, levothyroxine treatment may be initiated at a dose of 1.6 micrograms per kg per day *(www.bnf.nice.org.uk/drugs/levothyroxine-sodium/). [Evidence level 2++]*

Following the finding of SCH, there is insufficient evidence to recommend testing for TPOAb in pregnancy to guide care. Such an approach could also delay initiation of considered levothyroxine treatment. *[Evidence level 4]*

For SCH, levothyroxine may be initiated at doses of 1.0–1.20 micrograms per kg per day.[127,131,132] *[Evidence level 2+]*

Other international professional guidelines have delegated the choice of treatment of IH to the discretion of the caregiver,[133] with the 2014 European Thyroid Association guidelines also recommending consideration of treatment only in the first trimester of pregnancy,[132] when the greatest negative impact of IH on brain development is expected to possibly take place. If considering treatment of IH, potential consequences of overtreatment with levothyroxine should be considered (see below).

7.3 How should levothyroxine be titrated in pregnancy and adjusted after birth?

Recommendation	Evidence quality	Strength	Rationale for recommendation
TSH and fT4 concentrations should be checked every 4–6 weeks until 20 weeks of gestation then once again at 28 weeks of gestation.	**1++**	**A**	To mimic physiological changes in pregnancy and prospectively prevent abnormalities in thyroid function.
Aim to keep TSH below 2.5 mU/L while keeping the fT4 within the normal trimester-specific reference range.	**2+**	**C**	A commonly adopted approach is to maintain maternal serum TSH values in the lower half of the trimester-specific reference range. This reduces the risk of developing OH during pregnancy.
Following birth, for those who were already adequately replaced on levothyroxine preconception, revert to the preconception dose of levothyroxine two weeks postpartum.	**3**	**D**	TBG concentrations may take up to 4 weeks to return to pre-pregnancy levels following birth.
In women not taking levothyroxine preconception, stop levothyroxine following birth, and check thyroid function six weeks postpartum.	**3**	**D**	This enables reassessment of thyroid function and thyroxine requirements following reversion back to a non-pregnant state.

Following the initial empirical dose increase in women who were on levothyroxine prior to conception, up to 40% may require further dose adjustments during pregnancy.[130] Therefore, regular thyroid function monitoring is required, especially in the first 20 weeks of gestation, the period over which TBG concentrations rise, in conjunction with the other previously outlined physiological changes in pregnancy before steady-state is achieved. *[Evidence level 1++]*

The aim of dose titration to keep the TSH below 2.5 mU/L is to prevent even transient abnormalities in thyroid function tests by anticipating the normal dynamic changes of pregnancy that affect thyroid hormone requirements.

Thyroid function monitoring is also required to prevent the potential risks of overtreatment with levothyroxine. A Danish registry linkage study reported an association of maternal hyperthyroidism with a higher risk of ADHD being diagnosed in their children.[134] Naturally higher maternal fT4 concentrations during pregnancy in women who were not on levothyroxine replacement were also associated with lower birthweight[113] and increased offspring risk of autistic traits[124] in meta-analyses, as well as reduced brain cortical volumes and lower IQ (reduction in mean of 1.4–3.7 points) in a population-based study.[135] *[Evidence level 2+]*

However, no studies have reported on the neurodevelopmental effects of overtreatment with levothyroxine in a hypothyroid pregnant population. Nonetheless it is prudent to maintain fT4 concentrations within the normal trimester-specific reference range[108] *[Evidence level 4]* in addition to keeping the TSH concentration below 2.5 mU/L. *[Evidence level 2+]*

TSH suppression with normal free thyroid hormones was not associated with adverse effects.[31,32] *[Evidence level 2+]*

In women who experience nausea and vomiting of pregnancy, administration of levothyroxine at a time of day when they are less likely to be sick is a useful strategy. Alternatively, the daily levothyroxine dose can be split into two doses over this period of pregnancy to reduce the chances of the medication being incompletely absorbed. If they are unable to tolerate any oral levothyroxine, parenteral options (e.g. intravenous liothyronine) should be discussed with an endocrinologist. *[Evidence level 4]*

Following birth, maternal levothyroxine dosing should be restored to pre-pregnancy levels, if this provided adequate replacement, with a serum TSH measured 6–8 weeks thereafter. As TBG concentration may take up to 4 weeks to return back to pre-pregnancy levels following birth,[136] with reported associations between hypothyroidism and reduced breastfeeding success,[137] *[Evidence level 3]* it is reasonable to return to pre-pregnancy doses two weeks postpartum.[114] *[Evidence level 4]*

8. Thyroid antibodies and adverse pregnancy outcomes

8.1 Should women without thyroid disease be offered a thyroid peroxidase antibody (TPOAb) test in pregnancy?

Recommendation	Evidence quality	Strength	Rationale for recommendation
Routine testing for TPOAb in euthyroid women is not recommended in pregnancy.	**2++**	**B**	There is no intervention to improve outcomes in euthyroid TPOAb positive women so universal testing cannot be recommended.
If a woman is already known to be positive for TPOAb but euthyroid, they should be offered thyroid function test measurements in the first trimester (preferably at first contact with a healthcare professional, including primary care booking) and at 20 weeks of pregnancy to detect development of hypothyroidism (see Appendix 3).	**2++**	**C**	Large cohort studies have demonstrated progression to thyroid dysfunction during pregnancy in TPOAb positive women, especially during the first half of gestation when physiological thyroid demand is increasing.

Levothyroxine treatment is not recommended for women with TPOAb in the absence of thyroid dysfunction during pregnancy.	**1++**	**A**	There is no difference in outcomes with levothyroxine treatment.

The presence of TPO antibodies, even in women with a normal thyroid function, has been shown to be associated with an increase in adverse pregnancy outcomes, such as miscarriage (odds ratio, OR 3.90, 95% CI 2.48– 6.12; P < 0.001)[35,138] and preterm birth (OR 1.33 [95% CI, 1.15–1.56].[112] *[Evidence level 2+]*

There have been several randomised studies investigating whether levothyroxine treatment can improve pregnancy outcomes in women positive for TPOAb.[97,139] The largest trial on the subject (TABLET trial) randomised 952 euthyroid TPOAb positive women, with a history of either subfertility or miscarriage, to receive levothyroxine 50 micrograms once daily or placebo commenced preconception.[97] There was no improvement in live birth outcome at or beyond 34 weeks in those taking levothyroxine and no difference in any of the secondary pregnancy or neonatal outcomes. *[Evidence level 1++]*

However, around 7% of euthyroid women with TPOAb, went on to develop hypothyroidism, either within the one year of trying to conceive or during the first and second trimesters of pregnancy.[140] *[Evidence level 2++]*

Currently, there is no evidence that any treatment improves pregnancy outcomes for euthyroid women with TPOAb,[141] therefore, TPOAb testing should not be routinely offered in pregnancy. *[Evidence level 1+]*

Maternal passage of thyroid peroxidase antibodies across the placenta is not associated with clinically relevant fetal thyroid dysfunction.[142,143] *[Evidence level 3]*

9. Hyperthyroidism and thyrotoxicosis

Untreated or poorly controlled hyperthyroidism is associated with a number of adverse outcomes, but it remains unclear whether these consequences relate to maternal hyperthyroidism, to fetal hyperthyroidism (caused by transplacental transfer of thyroxine or stimulating TSH receptor antibodies [TRAb]) or to antithyroid drug treatment, which may cause fetal hypothyroidism as well as direct toxicity.[144] Large record linkage studies[145-148] have confirmed increased risks of pre-eclampsia, stillbirth, maternal admission to intensive care unit, lower birth weight and higher rates of attention deficit hyperactivity disorder and autism in children when comparing women with hyperthyroidism and control subjects.[149,150] Observational studies reported increased risks of intrauterine growth restriction, pre-eclampsia, preterm birth and maternal heart failure.[151-154] *[Evidence level 2++]*

The risk is directly related to control of maternal hyperthyroidism, both in terms of severity of hyperthyroidism and how soon in pregnancy euthyroidism is achieved.[144,155,156] *[Evidence level 2+]*

Maintenance of euthyroidism with optimal treatment throughout pregnancy coupled with adequate antenatal care, has not been associated with increased obstetric risks except for a possible residual risk of placental abruption[151,153] *[Evidence level 2+]* and antithyroid drug associated teratogenicity *[Evidence level 2++],* where applicable (see section 9.2).

9.1. How should women with Graves' disease be counselled before pregnancy?

Recommendation	Evidence quality	Strength	Rationale for recommendation
Pre-pregnancy counselling is recommended in women with hyperthyroidism to minimise maternal and fetal adverse outcomes.	**4**	**GPP**	The risks to the woman and fetus are directly related to control of hyperthyroidism early in pregnancy.
The option of definitive treatment with radioactive iodine or thyroidectomy should be discussed, especially in women with more severe disease. Following definitive treatment, women should wait at least six months before attempting to conceive. They should also have had serum fT4 within the reference range on two measurements three months apart.[157]	**2+**	**C**	Maintenance of euthyroidism during pregnancy is easier in women who have been rendered hypothyroid by definitive treatment. They would require levothyroxine replacement, with dose titrations in pregnancy. Further, the risk of teratogenicity with antithyroid drugs can be avoided.
A persistently increased TSH-receptor antibody (TRAb) level (usually taken as greater than 3 times the threshold for positivity) assessed around six months post-treatment is associated with increased risk of fetal Grave's disease and consideration may be given to further delay conception.	**3**	**D**	Retrospective studies show increased risks of fetal/neonatal Graves' disease with TRAb more than 3 times the assay threshold for positivity. TRAb levels decrease slowly following definitive treatment.
Women choosing to continue with antithyroid drugs while trying to conceive should be on propylthiouracil (PTU) in preference to carbimazole, at the lowest effective dose to maintain fT4 concentrations in the upper half of the reference range.	**2++**	**B**	PTU is associated with less teratogenic risks. Higher cumulative doses of antithyroid drugs are associated with increased risk of teratogenicity. The risk of inducing fetal hypothyroidism through transplacental passage of the drugs should be kept low by maintaining fT4 in the upper half of the reference range.

All women of childbearing age who develop hyperthyroidism should have a discussion regarding potential future pregnancy. The risks and benefits of all treatment options, including antithyroid drugs, radioactive iodine (^{131}I) administration or surgery should be discussed.[157] With definitive treatment, maintenance of euthyroidism with exogenous levothyroxine is simpler to achieve during pregnancy without risk of antithyroid drug-associated teratogenicity. *[Evidence level 2+]*

If the woman is on levothyroxine replacement following definitive thyroid ablation or thyroidectomy, then optimal TSH and fT4 concentrations should be achieved prior to trying conception, and they should be advised of an empirical dose increase upon conception, in accordance with guidance for treatment of autoimmune hypothyroidism (section 7.1).

Following radioiodine treatment, TRAb concentrations may rise,[152,153] increasing the risk of fetal Graves' disease caused by transplacental passage of maternal TRAb[154] even when maternal thyroid function tests are normal. *[Evidence level 2–]*

Hence, pregnancy should be delayed by 6 months.[158] Surgery may be the better option in women with high TRAb concentrations since antibody levels usually normalise within months following thyroidectomy,[150] and cure is immediate. However, the risks of surgery and lifelong need for levothyroxine treatment will need to be considered. *[Evidence level 3]*

If the woman continues on antithyroid drugs, propylthiouracil (PTU) is the recommended drug preconception and during the first trimester. A large cohort study found that higher cumulative doses of antithyroid drugs are associated with increased risk of teratogenicity.[155] *[Evidence level 2++]*

The fT4 concentrations should be maintained in the upper half of the normal range, and a low TSH concentration would be acceptable in this context. *[Evidence level 3]*

Consideration should be given to discontinuing antithyroid drugs preconception once euthyroidism (TSH in the reference range) is maintained for at least 6 months on a low dose.[51] Early discontinuation to reduce teratogenic risks need to be weighed against risks of a hyperthyroid flare in the periconception period which has the attendant risks of adverse effects in pregnancy (see Section 9.2. for a full discussion). *[Evidence level 3]*

9.2 What is the optimal care of women with Graves' hyperthyroidism in pregnancy?
(refer to summary in Appendix 4)

Recommendation	Evidence quality	Strength	Rationale for recommendation
When pregnant, where the woman has been euthyroid (TSH in the reference range) for 6 months or more on a low dose of an antithyroid drug (<10 mg CMZ or <200 mg PTU daily), consider discontinuing antithyroid drugs with close thyroid function monitoring.	**4**	**D**	Women who are in remission from Graves' disease are unlikely to relapse during pregnancy and the teratogenic risks of antithyroid drugs outweigh the risk of relapsed Graves' disease.
If antithyroid drug treatment is required, PTU is the recommended drug during early pregnancy. If a woman conceives on CMZ a switch to PTU should be made before 10 weeks' gestation, with an advised dose ratio of 1:20 (CMZ/PTU). There is no benefit of switching to PTU if a woman presents after 10 weeks gestation.	**3**	**D**	PTU is the preferred antithyroid drug during the period of organogenesis as it is associated with less teratogenic risks.

Women on antithyroid drugs should have thyroid function monitored every 2–4 weeks with measurement of serum TSH and fT4. Give consideration to fortnightly testing in the first half of pregnancy following the stopping of antithyroid drug treatment, when switching between antithyroid drugs and following dose adjustments.	**3**	**D**	Thyroid function may change rapidly during pregnancy in women on antithyroid drugs so regular testing is advisable.
Titration of antithyroid drugs should target fT4 concentrations in the upper half of the trimester-specific reference range.	**3**	**D**	Transplacental passage of antithyroid drugs may induce fetal hypothyroidism and should be avoided by maintaining fT4 in the high normal reference range. Serum TSH may remain low throughout pregnancy and fT4 testing is more informative in this situation.
Serial ultrasound scans to assess fetal biometry with umbilical artery Doppler at monthly intervals from 26–28 weeks is recommended in those who at any time during pregnancy had uncontrolled Graves' disease, required antithyroid drug treatment or had a TRAb level three times above the threshold of positivity.	**3**	**D**	Uncontrolled hyperthyroidism and high levels of TRAb are associated with intrauterine growth restriction and fetal Graves' disease. A TRAb level usually three times above the threshold of positivity is associated with increased risk of fetal/neonatal Graves' disease.
TRAb measurement in the first trimester is recommended in all women with a history of Graves' disease, even following definitive treatment. If it is above the threshold of positivity or if the woman is on antithyroid drugs, a further measurement at 20 and 28 weeks of gestation is recommended.	**3**	**D**	TRAb can remain raised even after definitive treatment. The fetal thyroid begins to produce appreciable amounts of thyroid hormone and can respond to transplacental TRAb from 18–20 weeks of gestation. TRAb levels usually gradually decline after 20 weeks of gestation and rarely increase beyond this point.
Neonates of women with known Graves' disease, of those receiving antithyroid medication during pregnancy and those with increased TRAb levels should have their thyroid function monitored soon after birth and at 1–2 weeks post-birth.	**3**	**D**	Transplacental TRAb or antithyroid drugs can induce neonatal hyperthyroidism or hypothyroidism, respectively. Early detection and treatment of the neonate can minimise adverse health consequences.

Treatment with antithyroid drugs (thionamides) represents the mainstay of treatment of active hyperthyroidism in pregnancy. Carbimazole (CMZ, used mainly in the UK), its active metabolite methimazole (MMI, used in the USA; 20 mg CMZ is equivalent to 15 mg MMI), and propylthiouracil (PTU) are the main antithyroid drugs. Minor adverse effects of antithyroid drugs, including skin rash,

occur in 3–5% of women. Serious adverse effects are rare and include agranulocytosis occurring in 0.15% with either drug and liver failure in 0.1%, the latter pertaining almost exclusively to PTU.[159]

Potential teratogenic effects have been mainly linked to CMZ/MMI, and to a lesser extent, PTU. CMZ/MMI may induce an embryopathy, including dysmorphic features, aplasia cutis, choanal and oesophageal atresia, abdominal wall defects, urinary and eye abnormalities, and ventricular septal defects. In addition to the background risks, teratogenic effects may be present in 2–4% of pregnancies if exposure occurs during 6–10 weeks of gestation.[156,160,161] *[Evidence level 2–]*

A meta-analysis has found CMZ/MMI exposure to be associated with an increased odds of congenital anomalies of 1.88 (95%CI 1.33–2.65) compared with no antithyroid drug exposure, with an escalating gradient of risk with increasing CMZ/MMI dose.[162] *[Evidence level 2++]*

PTU has been linked to less severe and potentially resolvable birth defects, including face and neck cysts and urinary tract abnormalities, which may occur in 2–3% of children exposed to the drug during early pregnancy.[160] These studies on both drugs do not take account of pregnancies terminated for congenital anomalies, and may therefore represent an underestimate of the teratogenic risk.

For PTU the largest studies conducted using national registries found odds ratios of 1.16–1.41 for congenital anomalies[160,162] but a meta-analysis of smaller studies showed no significant differences compared with the unexposed.[163] Of note, the range of defects associated with CMZ/MMI and PTU is different and they should be considered as two separate teratogens. The potential for a higher teratogenic risk with double exposure (the switching of one to the other drug during the first trimester) has not been borne out by a statistically significant increased odds in studies thus far, possibly due to small sample sizes.[160,162,163] If the woman is already past 10 weeks gestation there is limited benefit in switching from CMZ/MMI to PTU as the highest risk period for teratogenesis is over. *[Evidence level 3]*

If a woman has been euthyroid (TSH in reference range) for 6 months or more on low dose antithyroid drugs (defined as <10 mg CMZ daily or <200 mg PTU daily), consideration should be given to discontinuing antithyroid drugs, before the period of highest teratogenic risk (6–10 weeks of gestation).[51,161,164] This period of time also coincides with rising hCG concentrations which may exacerbate any residual hyperthyroidism, thus close thyroid function monitoring every 2 weeks until the mid-trimester of pregnancy (when hCG begins to decline) is recommended. *[Evidence level 3]*

Many women will require reducing doses of antithyroid medication as gestation progresses, and most can discontinue treatment in the late second or early third trimester of pregnancy as thyroid autoimmunity subsides.[165] If treatment with antithyroid drugs is still required beyond 20 weeks of pregnancy, a switch to CMZ should be considered in view of risk of PTU-associated hepatotoxicity.[30,51] A recommended conversion dose ratio is 20:1 (200mg PTU = 10mg CBZ). *[Evidence level 3]*

The lowest effective dose of antithyroid drugs should be used targeting serum fT4 at the upper half of the reference range (or total T4 at 1–1.5 times the upper limit of the non-pregnant reference range) in order to minimise the risk of fetal hypothyroidism from transplacental passage of the drug.[166,167] Titration should not be primarily based on TSH concentrations (which may be low), and there is no role for fT3 or total T3 measurements. *[Evidence level 2+]*

Women who have discontinued antithyroid drugs in pregnancy and maintained normal fT4 concentrations on two consecutive occasions 2–4 weeks apart following cessation of treatment may have less frequent thyroid function monitoring. This can be done at 4–8-week intervals for the remainder of pregnancy. *[Evidence level 3]*

Women in remission from Graves' hyperthyroidism who entered pregnancy whilst not taking antithyroid drugs and who have a low or undetectable TRAb level preconception or at pregnancy booking should have four weekly thyroid function testing until mid-trimester. If euthyroidism is maintained then thyroid function monitoring at 4–8 week intervals for the remainder of pregnancy is acceptable. *[Evidence level 3]*

The management of toxic nodular hyperthyroidism with antithyroid drug therapy in pregnant women is similar to Graves' hyperthyroidism except that it is associated with an even higher risk of fetal hypothyroidism since the fetal thyroid is not stimulated by TRAb. Thus, the dose of antithyroid drugs must be kept to the minimum with frequent thyroid function monitoring targeting the upper half of the reference range. *[Evidence level 3]*

Rare or infrequent situations

Block and replace regimens with high doses of antithyroid drugs and levothyroxine are not recommended as this increases both maternal and fetal risks. Furthermore, antithyroid drugs cross the placenta more efficiently than levothyroxine, and the fetal thyroid is very sensitive to antithyroid drugs, resulting in increased risks of fetal hypothyroidism and goitre.[51,150,168] In rare cases of isolated fetal hyperthyroidism a block replace regimen may be indicated.[169] *[Evidence level 3]*

In selected cases of severe maternal adverse effects to antithyroid drugs, or in cases of a large goitre with potential compromise of the airway, thyroidectomy may be indicated and ideally should be undertaken in the second trimester of pregnancy.[51] Thyroidectomy beyond 22 weeks of pregnancy is associated with increased risks of preterm birth[170] and should therefore be avoided where possible and undertaken with caution when it cannot be safely deferred. Close peri-operative management of fT4 and calcium concentrations is needed to minimise risks. *[Evidence level 3]*

Beta-adrenergic blocking agents such as propranolol, may be used temporarily for control of hyperthyroid symptoms as long as benefits outweigh risks. The lowest possible dose should be used for the shortest possible duration, to minimise potential risks of infants being small-for-gestational age at birth.[171] *[Evidence level 2–]*

Fetal monitoring

The half-life of PTU and CBZ/MMI are all less than 48 hours so exposure prior to the last menstrual period is unlikely to affect the fetus. The woman should be made aware of the limitations of ultrasonography at their 20 week fetal anomaly scan, as it can only detect some but not all anomalies associated with antithyroid drugs. Anomalies such as aplasia cutis, eye abnormalities and choanal atresia are very challenging to detect by ultrasonography.

Women with a history of hyperthyroidism but who have remained in remission without antithyroid drug treatment or any previous definitive radioiodine thyroid ablation/thyroidectomy, with undetectable circulating TRAb, and have been euthyroid during the pregnancy, do not require additional fetal surveillance. In these scenarios, a history of hyperthyroidism would not be considered a risk factor for having a small for gestational age fetus (SGA), consistent with another RCOG guideline.[172] *[Evidence level 3]*

In those who at any time during pregnancy displayed Graves' hyperthyroidism, required antithyroid drug treatment, or have detectable TRAb, there is an increased risk of intrauterine growth restriction and fetal Graves' disease. The underlying mechanisms may not only be placental-mediated, but

transplacental TRAb, antithyroid drugs and increased fetal thyroid hormones may disrupt metabolic regulation, growth and development of the fetus. Results of a 20-24 week uterine artery Doppler would not alter care and is therefore not necessary. Instead, serial ultrasonographic scans of fetal biometry with umbilical artery Doppler at monthly intervals from 26–28 weeks is recommended. Any abnormal findings should be managed in accordance with recommendations contained in the RCOG guidelines on the management of the SGA fetus.[172] *[Evidence level 3]*

Fetal and neonatal hyperthyroidism is estimated to occur in 1–5% of women with active or previous Graves' hyperthyroidism and is associated with significant morbidity and mortality.[173] Measurement of TRAb during early pregnancy is advised, and if increased a repeat measurement at 20 and 28 weeks of pregnancy is recommended.[51] The fetus is particularly at risk of fetal Graves' disease or in utero hyperthyroidism and growth restriction if TRAb levels are significantly raised (more than 3 times the threshold of positivity),[174,175] if maternal hyperthyroidism is uncontrolled and if pre-eclampsia or uteroplacental insufficiency is present. Increased fetal surveillance should include 2-4 weekly auscultation of fetal heart rate for fetal tachycardia (greater than 170 bpm persistent for more than 10 minutes)**.** With a significantly raised TRAb level, consider starting monthly ultrasonography earlier ~~starting~~ from 20 weeks gestation onwards (which is when appreciable endogenous fetal thyroid activity commences). This allows monitoring of fetal growth, amniotic fluid volume (severe polyhydramnios secondary to external compression of oesophagus by a goitre and reduced swallowing), presence of cardiac dysrhythmia and failure, fetal hydrops and, where expertise is available, presence of fetal goitre.[176,177] When fetal Graves' disease is detected or suspected, care should be undertaken in a multidisciplinary setting, including Fetal Medicine specialists. *[Evidence level 3]*

Peripartum care and neonatal hyperthyroidism

Timing and mode of birth is mostly dictated by obstetric indications. Maintaining euthyroidism will reduce maternal cardiovascular risks during labour and in the immediate post-partum period, and anaesthetic risks if assisted birth is required. Following birth, neonates of women with known Graves' disease, of those receiving antithyroid medication during pregnancy and those with increased TRAb levels should have their thyroid function monitored soon after birth and at 1–2 weeks post-birth for signs of neonatal hyperthyroidism. Neonatal hypothyroidism can also arise due to maternal over-treatment with antithyroid drugs, hence the need for careful antenatal thyroid function monitoring and titration. *[Evidence level 2–]*

9.3 What is the appropriate care of gestational transient thyrotoxicosis?
(refer to summary in Appendix 4)

Recommendation	Evidence quality	Strength	Rationale for recommendation
Severe nausea and vomiting alone in pregnancy should not prompt thyroid function testing in the absence of specific symptoms and signs of thyrotoxicosis or a personal history of thyroid dysfunction.	**3**	**D**	Nausea and vomiting are not symptoms of thyrotoxicosis. Specific symptoms and signs of thyrotoxicosis including weight loss prior to pregnancy, the presence of a goitre or ophthalmopathy, cardiac dysrhythmias as well as a personal or family history of hyperthyroidism point towards Graves' disease rather than

			gestational transient thyrotoxicosis.
In order to distinguish between Graves' Disease and gestational transient thyrotoxicosis consider carrying out TRAb and fT3 measurements.	**3**	**C**	New onset Graves' disease in pregnancy is likely to be associated with raised fT3 and TRAb measurement. These should be performed to avoid unnecessary starting of antithyroid drugs in women with gestational transient thyrotoxicosis.
Gestational transient thyrotoxicosis requires supportive treatment only.	**3**	**C**	In gestational transient thyrotoxicosis, there is no evidence that treatment with antithyroid drugs improves obstetric and fetal outcomes.

Gestational transient thyrotoxicosis is caused by high concentrations of hCG stimulating the TSH receptors of the thyroid gland[168] giving rise to low serum TSH and high fT4 concentrations. Where hCG concentrations are higher, for example, in multiple pregnancies, hydatiform mole and choriocarcinoma, gestational transient thyrotoxicosis is more common.[29,30] Since hCG levels peak around 10 weeks of gestation and subside by 18–20 weeks of gestation, gestational transient thyrotoxicosis usually presents in the first and early second trimesters of pregnancy. This condition is transient, self-limiting and is not associated with adverse pregnancy outcomes. *[Evidence level 2–]*

Thyrotoxicosis that is hCG-induced is more common in women who also experience hyperemesis gravidarum, but nausea and vomiting are not symptoms of hyperthyroidism, and each may occur independently. *[Evidence level 3]*

If a thyroid function test shows thyrotoxicosis, gestational transient thyrotoxicosis should be distinguished from Graves' disease. New onset Graves' disease requires prompt treatment in pregnancy (0.05% of pregnancies) and is far less common than gestational transient thyrotoxicosis (1–5% of pregnancies).[28,29,168] A number of clinical and laboratory features help in the distinction between the two conditions (Table 3). Clinical features, including palpitations, tremor, anxiety, heat intolerance and tachycardia, are non-discriminatory. A lack of symptoms of thyrotoxicosis and weight loss prior to pregnancy, the absence of a goitre, ophthalmopathy or a personal/family history of thyroid disease, as well as the presence of significant nausea and vomiting are more indicative of gestational transient thyrotoxicosis. TRAb and serum T3 concentrations are raised in Graves' disease but generally not in gestational transient thyrotoxicosis.[29,51,168] *[Evidence level 3]*

Table 3: Features distinguishing gestational transient thyrotoxicosis from Graves' hyperthyroid disease[29,51,168]

Feature	Gestational Transient Thyrotoxicosis (GTT)	Graves' hyperthyroid disease
Symptoms of thyrotoxicosis BEFORE pregnancy	No	Often
Symptoms of Hyperemesis Gravidarum (nausea/vomiting)	Yes (about 60% of GTT cases)	Often not present

Personal or family history of thyroid disease	Often absent	Present in about 50%[178]
Presence of goitre	No	Diffuse goitre in 90%[178]
Signs of thyroid eye disease	No	In around 20%[178]
fT3 concentration	Normal in 85%	Increased
TRAb measurement	Normal	Increased

Serum hCG concentrations are not useful in distinguishing the two conditions.[179] Where there is doubt, a repeat thyroid function test two weeks later, demonstrating a declining fT4 concentration without antithyroid treatment, would be supportive of gestational transient thyrotoxicosis. TSH concentrations will take longer to recover, often remaining suppressed, and are less helpful. *[Evidence level 3]*

Management of gestational transient thyrotoxicosis, if symptomatic, is largely supportive with anti-emetics, maintenance of hydration and correction of electrolyte imbalances if the women has hyperemesis gravidarum. Transient treatment with beta blockers may be used to control symptoms of thyrotoxicosis and tachycardia.[29,30] There is no evidence that treatment with antithyroid drugs improves obstetric and fetal outcomes in women with gestational transient thyrotoxicosis.[180] *[Evidence level 3]*

9.4 How should women with a history of hyperthyroidism be cared for in the postpartum period?

Recommendation	Evidence quality	Strength	Rationale for recommendation
A thyroid function test is recommended 6–8 weeks after birth in women with a history of pre-existing hyperthyroidism.	**3**	**C**	Increased autoimmunity postpartum increases the risk of relapsed Graves' disease.
Both CMZ and PTU are considered safe during breastfeeding and the lowest effective dose should be administered during the period of lactation with monitoring of the child's growth and development.	**3**	**C**	There is minimal transfer of these antithyroid drugs to breast milk. After initial surveillance for neonatal thyroid dysfunction is completed, thyroid function testing of breastfed babies is not recommended unless there are concerns about infant wellbeing.
Consideration may be given to administering the total daily dose of CMZ or PTU in two or three smaller doses a day.	**4**	**GPP**	Splitting the dose reduces peak circulating concentrations.

The most common cause of thyrotoxicosis in the postpartum period in the general obstetric population is postpartum thyroiditis (see Section 11). However, the increased autoimmunity in the postpartum period is also associated with a 3–4 times higher risk in the incidence of new onset Graves' hyperthyroid disease[165] and higher rates of relapsed Graves' disease in those with a pre-existing diagnosis prior to pregnancy.[181] Management differs by aetiology, and in this section, only the management of pre-existing hyperthyroidism and Graves' disease is discussed.

Antithyroid drugs are the preferred therapeutic option in postpartum hyperthyroidism since the administration of radioactive iodine is difficult in view of radiation protection guidance and surgery is

invasive, and both may pose practical difficulties in women with young children.[29,30]

Observational studies indicate that both CMZ (up to a daily dose of 20 mg) and PTU (up to a daily dose of 450 mg) are safe during breastfeeding.[182,183] CMZ[184] and to a lesser extent PTU[185] are transferred into breastmilk in small amounts: 0.1–0.2% and 0.007–0.077% of the ingested amount, respectively. *[Evidence level 3]*

Antithyroid drugs in breastmilk may delay the manifestation or reduce the risk of neonatal hyperthyroidism caused by persistent *in utero*-derived TRAb. The growth and development of breastfed infants of women taking antithyroid drugs should be monitored, but routine assessment of thyroid function (beyond the initial surveillance for neonatal thyroid dysfunction) in the infant during breastfeeding is not required, unless antithyroid drug doses exceed the recommendations above[51] or there are concerns about infant wellbeing. *[Evidence level 3]*

10. Thyroid nodules and thyroid cancer

The prevalence of thyroid nodules in pregnancy based on ultrasound studies in areas with mild-to-moderate iodine deficiency varies between 15% and 21%,[40,41] but the incidence of clinically apparent nodules presenting in pregnancy in non-iodine-deficient areas is likely to be under 1%.[39] *[Evidence level 2+]*

Ultrasound-detected nodules are more common with increasing parity and age,[40,41] and may increase in size during pregnancy.[40,186] Thyroid cancer in association with pregnancy is very rare, with a prevalence of 14 in 100 000[187] and is more likely to be diagnosed postpartum than at other times in pregnancy.[39,187] *[Evidence level 2+]*

10.1 What is the management of thyroid nodules in pregnancy?

Recommendation	Evidence quality	Strength	Rationale for recommendation
In all women with new or enlarging clinically detectable thyroid nodules or goitre in pregnancy, check thyroid function and refer to an appropriate specialist for assessment.	**3**	**D**	To ensure appropriate management of possible thyroid dysfunction, and airway obstruction in pregnancy and labour, as well as exclude malignancy.
If there is suspicion of malignancy on ultrasound, a fine needle aspiration can be safely performed at any gestation.	**2+**	**B**	Proven diagnostic use and safety in pregnancy.
If thyroid surgery is required this should ideally be performed between 14–22 weeks of gestation.	**3**	**C**	To reduce the risk of miscarriage and preterm labour.
Women with an enlarged thyroid in pregnancy should be reviewed by an obstetric anaesthetist.	**3**	**D**	To manage possible airway obstruction and anticipate risk of a difficult intubation in the event a general anaesthetic is required.

Women with compressive symptoms from thyroid enlargement should be referred urgently to an ENT surgeon/Endocrinologist (depending on local expertise) for airway assessment and consideration of

surgical intervention. Surgical intervention should ideally be made between 14–22 weeks' gestation, where possible, to minimise maternal and fetal morbidity, pregnancy loss and preterm birth.[170,188] *[Evidence level 3]*

The primary aims in care when a new thyroid nodule is diagnosed are three-fold: to assess local symptoms, and to exclude malignancy and hyperthyroidism. Ultrasound is the most sensitive test for detecting thyroid nodules, measuring their dimensions, identifying their content and evaluating any associated changes in the thyroid gland.[189] Radioactive agents should be avoided for diagnostic or therapeutic purposes in pregnancy.[190] If fine needle aspiration is required for diagnostic purposes this may be performed at any gestation.[133,191-193] *[Evidence level 2+]*

10.2 What is the effect of pregnancy on the risk of progression and recurrence of thyroid cancer?

Recommendation	Evidence quality	Strength	Rationale for recommendation
There is no difference in the rate of recurrence or long-term survival of women with well-differentiated thyroid cancer identified during pregnancy compared with those diagnosed outside of pregnancy.	**2+**	**B**	Current literature including meta-analysis of cohort studies.

Studies have compared the diagnostic features and prognosis of women diagnosed with differentiated thyroid cancer either during pregnancy or within the first year postpartum to non-pregnant women.[194-198] All are retrospective, and the size of many of the studies was limited or did not use the contemporary tools for the detection of recurrence. Most clinical outcome data show no difference in the rate of recurrence or long-term survival of women following treatment for well-differentiated thyroid cancer identified during pregnancy.[191] A meta-analysis[199] with a total of 406 329 cases found that women who developed thyroid carcinoma during pregnancy did not exhibit a significantly increased risk of lymphatic metastasis (OR 0.94, 95% CI 0.53–1.67) or distant metastasis (OR 1.03, 95% CI 0.86–1.24). *[Evidence level 2+]*

Generally, surgery for most common thyroid cancer diagnosed in pregnancy can be deferred until after birth unless there is substantial growth, significant airway compression, or rapidly progressive disease. *[Evidence level 3]*

11. Postpartum thyroiditis

Postpartum thyroiditis (PPT) is defined as the development of thyroid dysfunction, excluding thyroid disease, within the first 12 months following a pregnancy in a previously euthyroid woman.[200] This is an autoimmune disorder associated with antibodies to TPO and thyroglobulin (Tg),[201] caused by a reactivation of the immune system following the relative immune suppression during pregnancy.[202]

PPT occurs in 5–10% of unselected pregnancies.[203] Women with other autoimmune disorders are at increased risk, in particular, those with type 1 diabetes mellitus,[204] SLE[100] and a previous history of Graves' disease.[205] PPT may also occur in those with Hashimoto's thyroiditis[206] or with a personal or family history of thyroid disease.[202] Overall, 30–50% of women with positive TPOAb develop PPT with higher risk in those with higher TPO antibody concentrations.[207] *[Evidence level 3]*

The classical form of PPT is triphasic with an initial thyrotoxic phase followed by a transient hypothyroid phase and then a return to euthyroidism. The clinical course is variable with 20–40% of

women exhibiting the classical form, 20–30% developing only thyrotoxicosis and 40–50% presenting with isolated hypothyroidism.[202,207] The thyrotoxic phase usually occurs between 2 and 6 months postpartum but may present up to 12 months following birth. The hypothyroid phase typically presents between 3–12 months postpartum and results in permanent hypothyroidism in up to 50%.[51,208,209] Risk factors for permanent hypothyroidism include multiparity, higher concentrations of TPO antibodies, greater maternal age, more severe hypothyroidism, thyroid hypoechogenicity on ultrasound scanning and a history of pregnancy loss.[51,202,210] The risk of relapse of PPT with subsequent pregnancies is as high as 70%, especially in TPOAb-positive women.[202] Some studies have indicated a link between TPOAb positivity,[211-213] PPT[214] and postpartum depression, but an RCT of levothyroxine prophylaxis in TPOAb-positive women did not lower rates of postpartum depression.[215] *[Evidence level 1+]*

11.1 How should postpartum thyroiditis be diagnosed?

Recommendation	Evidence quality	Strength	Rationale for recommendation
Routine testing for PPT is not recommended.	**4**	**D**	This condition is mostly self-limiting.
In women with risk factors for PPT who experience symptoms of thyrotoxicosis, thyroid function tests should be performed.	**4**	**D**	Case series have shown higher risk of PPT in women with these risk factors and symptoms.
To confirm the diagnosis of PPT in the presence of an abnormal thyroid function test, perform serial thyroid function testing every 6 weeks with symptom assessment, and exclude other aetiologies. At any point, if thyroid function tests show thyrotoxicosis measure TRAb and consider isotope scans to distinguish between Graves' disease and PPT.	**2–**	**C**	PPT is characterised by evolving clinical features and biochemistry indicative of thyroid dysfunction. Increased TRAb and diffuse uptake of isotopes are consistent with Graves' disease.

The thyroidal inflammation in PPT is usually painless and many women are asymptomatic, but a small diffuse goitre may be present. During the thyrotoxic phase, irritability, palpitations or heat intolerance may develop.[51,202,216] The hypothyroid phase is more frequently symptomatic and cold intolerance, dry skin, fatigue and concentration difficulties may be present.[217] TPOAb-positive women with PPT usually have more symptoms than those without raised concentrations of TPOAbs.[218]

The major challenge is to distinguish thyrotoxicosis caused by PPT from de novo or recurrent Graves' disease in the postpartum period. Thyrotoxic symptoms during the first 3 months postpartum are more likely due to PPT and those presenting 6 months following birth are often caused by Graves' disease.[219] Ophthalmopathy, a large goitre with bruit, and raised TRAb levels confirm Graves' disease whereas a raised T4:T3 ratio is found in PPT. Uptake of radioactive isotope (Technetium [^{99m}Tc] or radioiodine [^{123}I]) is increased in Graves' disease and low in PPT. Both isotopes may be used in breastfeeding women as long as the breastmilk is discarded for at least 3 days after the radioisotope investigation.[51,202,220] Thyroid ultrasonography usually reveals a non-homogeneous hypoechogenic texture[221] and histopathological evaluation demonstrates lymphocytic infiltration in PPT.[202]

11.2 What is the optimal care of postpartum thyroiditis if diagnosed?

Recommendation	Evidence quality	Strength	Rationale for recommendation
Antithyroid drugs are not indicated in the management of the thyrotoxic phase of PPT.	**2+**	**B**	The thyrotoxic phase is caused by transient destructive thyroiditis. Antithyroid drugs inhibit thyroid hormone production and cannot address the pathology of PPT.
Consider treatment of symptomatic women in the thyrotoxic phase with beta-blockers.	**4**	**C**	Beta blockers are very effective in controlling symptoms of thyrotoxicosis, if required. Propranolol and metoprolol are safe in breastfeeding.
Levothyroxine replacement is appropriate for women who are very symptomatic during the hypothyroid phase of PPT or actively trying to become pregnant.	**4**	**D**	Levothyroxine is a safe and effective treatment to relieve symptoms, including during breastfeeding. If planning pregnancy, optimal control of thyroid function is associated with improved pregnancy outcomes.
Those who are not treated can be managed expectantly with thyroid function monitoring every 6 weeks until restoration of euthyroidism.	**4**	**D**	PPT usually resolves spontaneously but a proportion of women will develop permanent hypothyroidism.
Following restoration of euthyroidism, monitor serum TSH annually in women with a history of PPT as they continue to be at risk of developing permanent hypothyroidism.	**2++**	**C**	Approximately 50% of women with a history of PPT develop permanent hypothyroidism.
In women with a history of PPT, test for thyroid dysfunction when planning to get pregnant and as soon as possible in pregnancy.	**2++**	**C**	Optimal control of thyroid function preconception and in pregnancy is associated with improved pregnancy outcomes.
There is insufficient evidence to recommend levothyroxine prophylaxis, or either iodine or selenium supplementation to prevent or treat PPT.	**1–**	**B**	The evidence from small RCTs is inconclusive.

If levothyroxine is started in the hypothyroid phase, tapering off the dose may be attempted after 12 months, although this is not appropriate if women are actively trying for pregnancy and individualised treatment decisions should be taken.[51,202] In view of the relatively high risk of development of permanent hypothyroidism *[Evidence level 2++]*, serum TSH should be monitored annually in women with a history of postpartum thyroiditis.[208,222] Additional testing may be appropriate when they are trying to conceive and as soon as possible when pregnant.

Two RCTs of levothyroxine or iodine supplementation during and after pregnancy in TPOAb-positive women have failed to demonstrate efficacy in prevention of PPT.[223,224] One single trial has indicated potential benefit of selenium supplementation in preventing PPT in TPOAb-positive women.[225] However, there is insufficient evidence to recommend its routine use in this setting.

12. Recommendations for future research

- Further controlled trials of iodine supplementation from early gestation in pregnant women in the UK and in other iodine replete or mildly iodine deficient populations, with follow up of the children for measurement of neurocognitive and behavioural outcomes.
- Cost-benefit analyses of universal versus risk-based thyroid function testing in different health settings and subpopulations.
- Treatment of subclinical hypothyroidism and isolated hypothyroxinaemia from preconception or early pregnancy for improvement of pregnancy and child outcomes, especially in obstetric populations deemed at high-risk due to co-morbidities.
- Clinical trials comparing different management approaches of hyperthyroidism before and during pregnancy, and evaluating impact on obstetric and fetal outcomes

13. Auditable topics

- At least 95% of thyroid function tests performed and reported in pregnancy should have used or quoted trimester-, population-, and manufacturer- specific reference ranges, where available.
- At least 90% of women with risk factors for thyroid dysfunction (in accordance with this guideline, section 6) should have been offered testing during the first trimester with thyroid function tests comprising TSH and fT4 simultaneously.
- Levothyroxine treatment for OH and SCH should be offered at appropriate TSH thresholds in accordance with this guideline on 95% of occasions.
- At least 90% of women who were already on levothyroxine treatment pre-pregnancy for hypothyroidism should have been counselled before pregnancy or in early pregnancy to empirically increase their levothyroxine dose by an appropriate amount as soon as possible in pregnancy.
- Following each dose change of levothyroxine, repeat thyroid function tests should be performed in 4-6 weeks and levothyroxine dose titrated in accordance with this guideline on 95% of occasions.
- At least 90% of women who conceived on CMZ should have been advised to either stop treatment or change to PTU before 10 weeks of gestation, as clinically appropriate, in accordance with this guideline.
- In women on antithyroid drugs in pregnancy, frequency of thyroid function monitoring and appropriate titration of medication should be conducted in accordance with this guideline (to maintain fT4 concentrations in the upper half of the trimester-specific reference range) on 95% of occasions.

14. Useful links and support groups

British Thyroid Association (https://www.british-thyroid-association.org/)
British Thyroid Foundation (https://www.btf-thyroid.org/)
The UK Iodine group (https://www.ukiodine.org/)

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Appendix 1: Explanation of grades and evidence levels

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

A At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good Practice Points (GPP)

✓ Recommended best practice based on the clinical experience of the guideline development group.*

*on the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated by ✓ **or GPP**. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

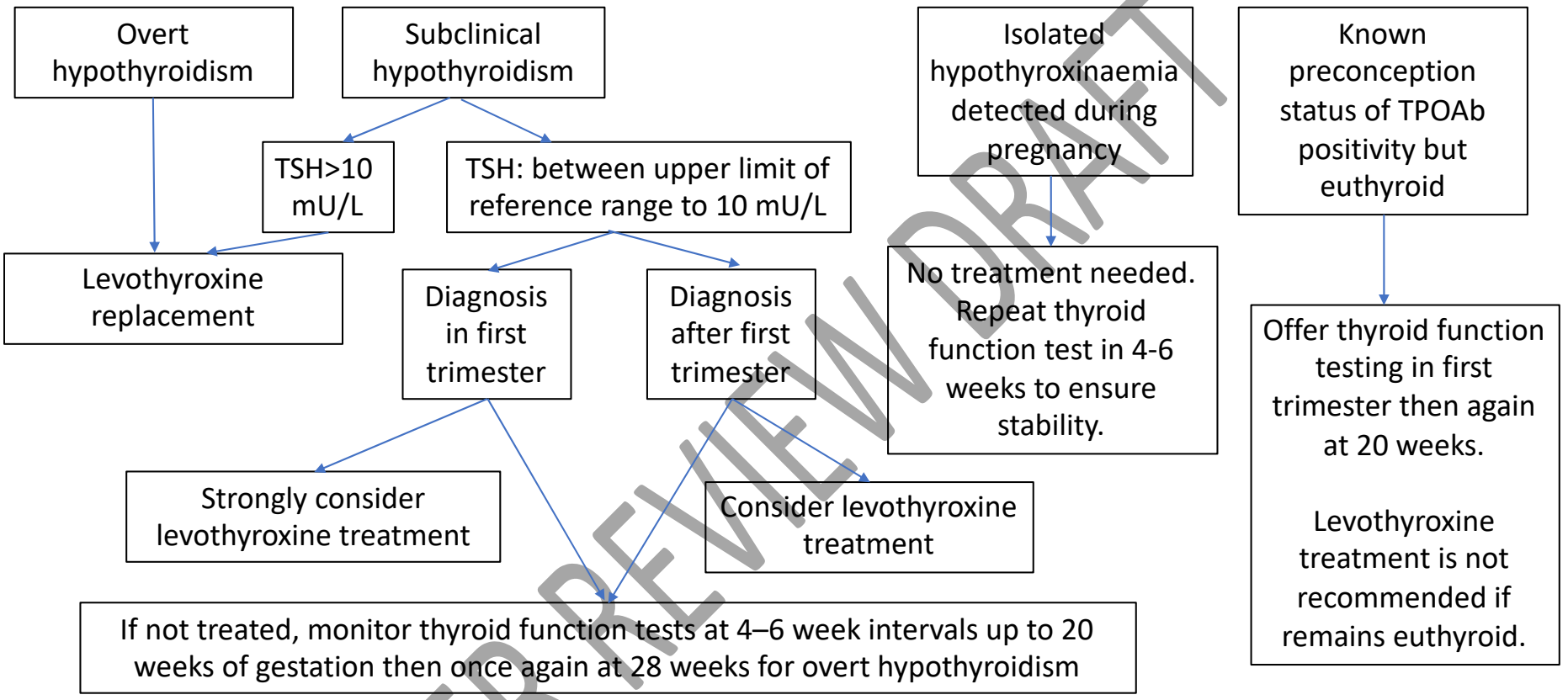
Appendix 2.

Where trimester-, population-, and manufacturer- specific reference ranges is not issued by the laboratory, these thyroid function reference ranges in pregnancy by different manufacturers of assays commonly used in the UK may be applied[47]

	Abbott Architect	Beckman Access/Dxl	Roche Cobas/ Elecsys	Siemens Advia Centaur
First Trimester	TSH: 0.09–3.46	TSH: 0.06–3.32	TSH: 0.12–4.10	TSH: 0.06–3.67
	fT4: 10.9–18.7	fT4: 8.7–15.6	fT4: 11.6–20.3	fT4: 11.9–19.2
Second Trimester	TSH: 0.32–3.31	TSH: 0.32–3.31	TSH: 0.11–4.26	TSH: 0.47–4.46
	fT4: 9.7–17.2	fT4: 6.8–12.4	fT4: 9.9–17.7	fT4: 11.6–17.6
Third Trimester	TSH: 0.38–4.34	TSH: 0.34–5.02	TSH: 0.50–4.71	TSH: 0.60–4.60
	fT4: 8.8–14.9	fT4: 6.0–11.7	fT4: 8.7–15.2	fT4: 9.6–16.5

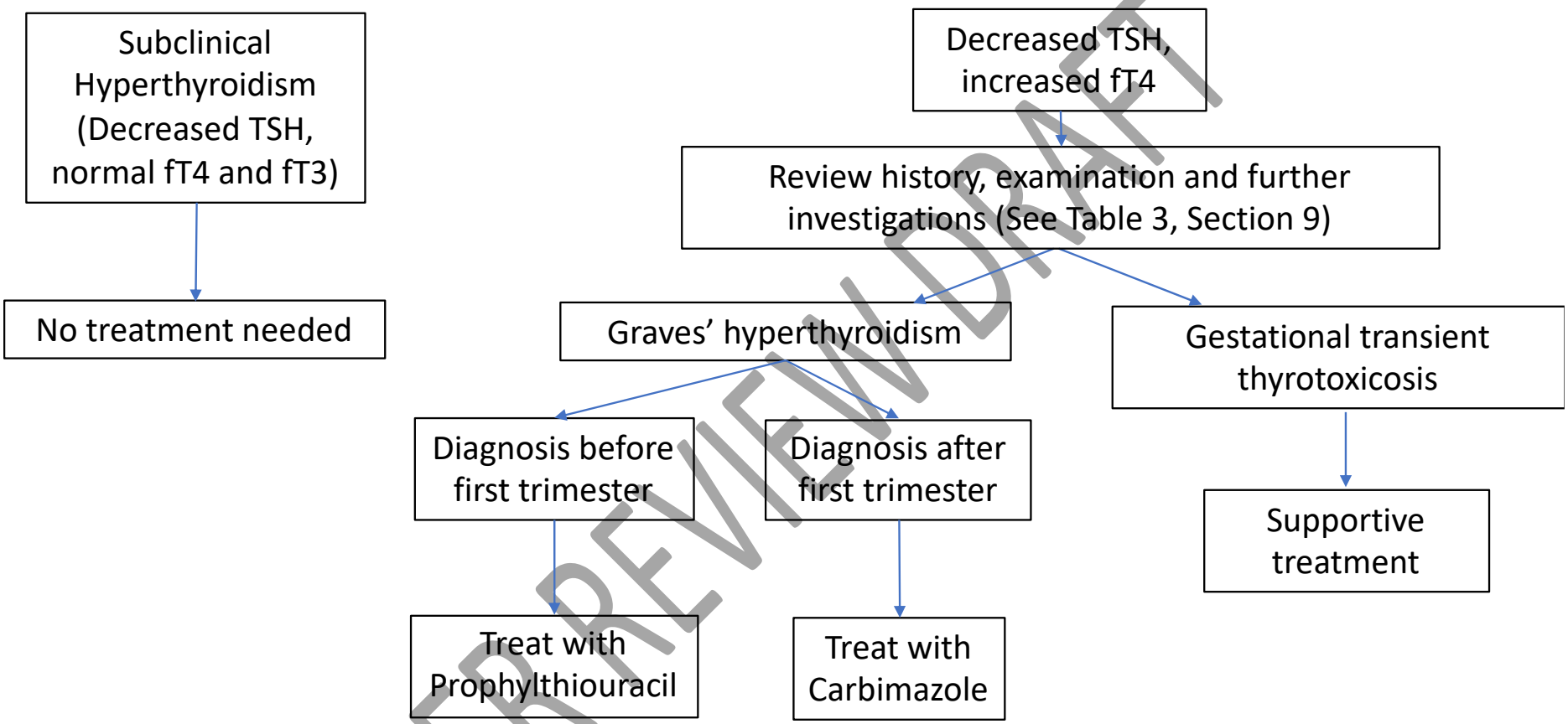
Median upper and lower limit of thyroid stimulating hormone (TSH; expressed in mU/L) and free thyroxine (fT4; expressed in pmol/L) for studies published between January 2000 to December 2020. Articles in which thyroid hormones were measured using one of four assay methods: Abbott Architect, Beckman Access or Dxl, Roche Cobas or Elecsys, and Siemens Advia Centaur, were selected. Only studies that reported reference intervals as 2.5–97.5 centiles with gestational age information at time of blood sampling were included. Studies were excluded if they were not in English, had less than 120 participants, did not exclude women with positive antibodies or thyroid disease, or were conducted in areas with excess or deficient iodine nutrition status.

Appendix 3. Management of hypothyroidism and related disorders in pregnancy



Note: Universal testing for thyroid dysfunction and Anti-TPO is not recommended in pregnancy

Appendix 4. Management of hyperthyroidism, thyrotoxicosis and related disorders diagnosed during pregnancy



Note: Universal testing for thyroid dysfunction is not recommended in pregnancy

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All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from:

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.