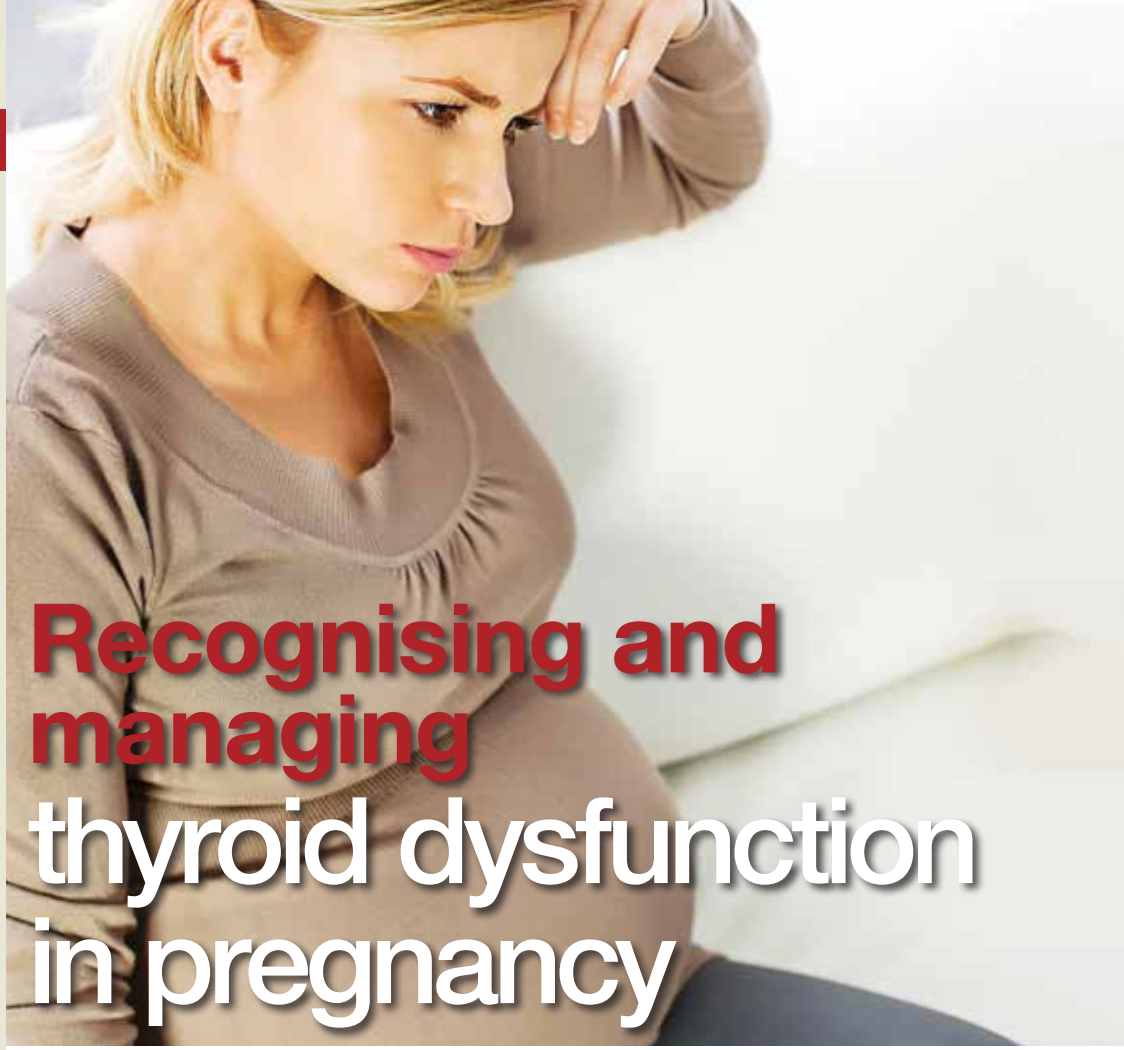
MedicineToday 2014; 15(12): 47-54

PEER REVIEWED FEATURE
2 CPD POINTS



Recognising and managing thyroid dysfunction in pregnancy

Key points

- Thyroid hormone production and metabolism change with pregnancy.
- Iodine supplementation is advised in most women during pregnancy to meet guideline recommendations for nutritional intake.
- All women should be screened for thyroid dysfunction using a thyroid-stimulating hormone measurement during early pregnancy. At-risk groups will require more frequent monitoring throughout the pregnancy.
- Women taking thyroxine replacement before pregnancy will usually require a dose increase of 30 to 50% in the first trimester.
- Thyroxine replacement should be taken separately to other vitamins, including iron and calcium supplements, because binding can occur, decreasing the efficacy of absorption.
- It is essential that women with thyroid dysfunction before or during pregnancy be seen by their GP in the postpartum period for follow-up assessment of their thyroid function.

© ISTOCKPHOTO/SKYNESHER. MODEL USED FOR ILLUSTRATIVE PURPOSES ONLY.

VERONICA A. PREDA BSc(Med), MB BS(Hons), MPH
DIANA L. LEAROYD MB BS(Hons), PhD, FRACP

During pregnancy the production and metabolism of thyroid hormone change. Appropriate monitoring of thyroid-stimulating hormone levels with trimester-specific reference ranges is essential to avoid adverse effects in the pregnant woman and fetus.

The management of thyroid dysfunction in pregnant women has received much attention since the recent publication of three comprehensive sets of guidelines from the USA and Europe.[1-3] Debate still continues as to whether all pregnant women, or even all women planning pregnancy, should be screened for thyroid dysfunction with measurement of their thyroid-stimulating hormone (TSH) levels. It is important to identify significant thyroid dysfunction at crucial stages of pregnancy, especially hypothyroidism in the first trimester, which can cause adverse fetal outcomes.[4-6]

The responsibility of care of pregnant women with thyroid dysfunction often falls between the GP, endocrinologist and obstetrician. There needs to be consensus by the managing team as to who is assuming primary responsibility for organising thyroid function tests (TFTs). The results of these tests can then be forwarded to the endocrinologist, who can offer guidance for the patient and all clinicians involved throughout the pregnancy.

Thyroid dysfunction in pregnancy is most commonly detected incidentally either by TSH screening in asymptomatic women with no

Dr Preda is a Fellow in the Department of Endocrinology at the Royal North Shore Hospital, Sydney, and an Associate Lecturer at the Faculty of Medicine, The University of Sydney, Sydney. Associate Professor Learoyd is an Endocrinologist at the Royal North Shore Hospital, Sydney, and an Associate Professor at the Faculty of Medicine, The University of Sydney, Sydney, NSW.

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2014.

1. PATIENTS AT HIGH RISK OF HYPOTHYROIDISM WHO SHOULD BE SCREENED PRECONCEPTION[1]

- Maternal age >30 years
- Thyroid peroxidase antibody (TPOAb) positivity
- Family history of thyroid dysfunction
- History of head and neck irradiation
- Type 1 diabetes
- Other known autoimmune disease
- History of unexplained miscarriage
- History of preterm delivery
- History of childhood malignancy
- History of infertility
- Living in an area of known iodine insufficiency

history of thyroid disorders or by the routine checking of TFTs in women with a known history of thyroid disease.[7] Most clinicians would recommend TSH screening just before conception in women with a known history of any thyroid disorder. Even if the TSH level is normal at or before conception, it is the view of the authors that TSH levels should be rechecked at about four weeks of gestation in all women. Case-detection based on risk factors misses a very high proportion of thyroid abnormalities in pregnant women compared with universal screening. The guidelines suggest screening all patients at high risk of hypothyroidism (Box 1).[1]

The causes and management of thyroid dysfunction in pregnant women are discussed in this article.

PHYSIOLOGICAL CHANGES IN NORMAL PREGNANCY AND EFFECTS ON TFT PARAMETERS

The first trimester of pregnancy is associated with a rise in concentration of serum thyroxine-binding globulin (TBG) because oestrogen increases TBG production and sialylation, which results in decreased clearance of TBG, along with stimulation of the TSH receptor by human chorionic gonadotrophin (hCG).[8] hCG has a common α-subunit and a unique β-subunit, which has considerable similarity to the β-subunit of TSH. Therefore, beta hCG acts as a weak stimulus to the TSH receptor.[9]

TABLE 1. TRIMESTER-SPECIFIC RANGES AND TARGETS[1,2]

Trimester	TSH normal ranges (mIU/L)
First	0.1 to 2.5
Second	0.2 to 3.0
Third	0.3 to 3.0

ABBREVIATION: TSH = thyroid-stimulating hormone.

Often during pregnancy there is a minor reduction in TSH levels with normal thyroxine (T_4) and tri-iodothyronine (T_3) levels and negative thyroid antibodies (including negative thyroid receptor antibodies [TRAb]). There are also normal physiological changes that occur during pregnancy that affect thyroid homeostasis, predisposing a woman to thyroid deficiency. These include increased renal excretion of T_4, transfer of T_4 to the fetus and breakdown of T_4 by placental deiodinases.[4,10]

IODINE INTAKE DURING PREGNANCY

Iodine requirements are greater during pregnancy because of increased maternal T_4 production, which is required to maintain maternal euthyroidism, and increased renal iodine clearance. The World Health Organization global recommendations are that pregnant and lactating women should ingest 250 µg/day of iodine from supplements and dietary sources.[11] When planning a pregnancy, women will usually need to supplement their diet with an oral iodine supplement of 150 µg/day.[1,12]

Large iodine doses (>1000 µg/day) from dietary sources or very high-dose supplements should be avoided due to the risks of fetal hypothyroidism and goitre. Less than 50% of pregnant women have adequate knowledge about the need for iodine supplementation in pregnancy.[13]

TRIMESTER-SPECIFIC TFT RANGES IN PREGNANCY

Laboratories should quote their own trimester-specific TSH reference ranges for pregnancy. Large population studies, which included more than 13,000 pregnant women, have established the reference range for TSH levels in the first trimester as 0.03 to 2.99 mIU/L.[14,15] The ranges given in Table 1 for each trimester are those recommended by the American Thyroid Association (ATA) guidelines.[1]

Measurements of direct free T_4 may be unreliable during pregnancy, especially if certain laboratory methods are not adopted (i.e. online extraction, liquid chromatography and tandem mass spectrometry). The decreased albumin concentrations during pregnancy can cause the immunoassay to be inaccurate.[16] Measurement of TSH levels remains more accurate.

If the TSH level is abnormal then free T_4 and free T_3 levels should be measured, along with TRAb (for Graves' disease), thyroid peroxidase antibody (TPOAb; also known as thyroid microsomal antibody [TMAb]) and thyroglobulin antibody (TgAb) levels (for Hashimoto's disease). This is to clarify if there is autoimmune thyroid disease and, if present, to assess the severity. Total T_4 measurements are not routinely performed in Australia.

HYPOTHYROIDISM IN PREGNANCY

Iodine deficiency can cause hypothyroidism. With the availability of trimester-specific reference ranges in routine clinical practice, milder forms of thyroid dysfunction (such as subclinical hypothyroidism and maternal isolated hypothyroxinaemia) are being diagnosed in about 15% of pregnant women.[10] The most common cause of overt hypothyroidism in pregnancy is chronic autoimmune thyroiditis, known as Hashimoto's disease. This and other less common causes are listed in Box 2.

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2014.

2. CAUSES OF PREGNANCY-RELATED HYPOTHYROIDISM

Common

- Hashimoto's disease – autoimmune thyroid disease
- Iodine deficiency (although uncommon in Australia)

Less common

- Post-thyroid surgery hypothyroidism
- Central hypothyroidism/ hypopituitarism

Profound hypothyroidism (elevated TSH and reduced free T_4 levels) is unusual in pregnancy due to the reduced fertility rate and high rate of first trimester spontaneous abortion in affected women.[17] Adverse associations with hypothyroidism in pregnancy are listed in Box 3.[18,19]

Overt hypothyroidism, subclinical hypothyroidism and maternal isolated hypothyroxinaemia

All pregnant women with a TSH level of more than 10 mIU/L should be treated for overt hypothyroidism with thyroxine replacement, regardless of the free T_4 level. Pregnant women with TSH levels between 2.5 and 10 mIU/L should also be treated. However, those with isolated low free T_4 levels need no treatment if the TSH levels are normal, as this is maternal isolated hypothyroxinaemia.[1,2]

Treatment with thyroxine replacement is also required for pregnant women with positive TPOAb or TgAb results and subclinical hypothyroidism (i.e. TSH level between 2.5 and 10 mIU/L with normal free T_4 level; Table 2).[2,20]

Subclinical hypothyroidism is associated with adverse fetal outcomes.[19,21] The guidelines from the American Endocrine Society recommend treatment of affected women as there is evidence that thyroxine replacement in such circumstances may reduce obstetric complications.[1] The most recent European guidelines recommend thyroxine therapy for maternal subclinical hypothyroidism.[3] The decision to treat euthyroid women with elevated TPOAb or TgAb levels and monitor for the development of hypothyroidism is subject to debate. The American Thyroid Association has not recommended against therapy.[1,2]

Treatment should be with conventional thyroxine rather than with alternative preparations (such as T_3 or thyroid extract) and trimester-specific TSH targets are the goal of therapy. TSH level cut-offs are lower in pregnant women than in nonpregnant women. Patients taking T_3 should stop taking it when they become pregnant and change to thyroxine during pregnancy because T_3 is not thought to cross the placenta. Maternal transfer of thyroxine

3. ADVERSE ASSOCIATIONS WITH HYPOTHYROIDISM IN PREGNANCY[18,19]

- Spontaneous abortion
- Premature labour
- Low birthweight
- Placental abruption
- Pre-eclampsia
- Cognitive impairment in the offspring
- Postpartum haemorrhage

during the first trimester is required until the fetus makes its own thyroid hormones during the second and third trimesters. If patients have been stabilised on a dose of thyroxine, most will need a 30 to 50% increase in dose by four to six weeks of gestation. If dose adjustments are being made, more frequent biochemical testing will be necessary until target levels are reached.

If treatment is not required initially, such as in cases of subclinical hypothyroidism, the patient should have monthly monitoring for overt hypothyroidism until 20 weeks of gestation and at least once between 26 and 32 weeks of gestation.

Hashimoto's disease

Hashimoto's disease is the most common cause of overt hypothyroidism in pregnant

TABLE 2. HYPOTHYROIDISM: ASSOCIATED BIOCHEMISTRY AND TREATMENT RECOMMENDATIONS [1-3,20,21]

Thyroid status and disease	TSH level	T4 level	TPOAb or TgAb status	Treatment recommended (thyroxine)
Euthyroid, positive TPOAb	Normal	Normal	Positive	Insufficient evidence – no
Maternal isolated hypothyroidism	Normal	Low	Negative	No
	Normal	Low	Positive	No
Subclinical hypothyroidism	Elevated	Normal	Negative	Insufficient evidence – ?yes
	Elevated	Normal	Positive	Yes
Overt hypothyroidism	Elevated	Low	Negative	Yes
	Elevated	Low	Positive	Yes

ABBREVIATIONS: T_4 = thyroxine; TgAb = thyroglobulin antibody; TPOAb = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone.

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2014.

4. CAUSES OF PREGNANCY-RELATED HYPERTHYROIDISM

Common
- Gestational transient thyrotoxicosis (hCG-mediated hyperthyroidism)
- Graves' disease

Less common
- Toxic multinodular goitre
- Toxic adenoma
- Thyroiditis
- Struma ovarii

women and is characterised biochemically by an elevated TSH level, reduced free T_4 level and positive TPOAb and/or TgAb. Patients already taking thyroxine for autoimmune hyperthyroid disease may have changes in TFTs after conception, and may require an early increase in the thyroxine dose. An automatic increase of 20 to 30% in the dose is usually recommended when pregnancy is confirmed. However, some patients on low doses require no change as the thyroid gland seems to adjust, whereas others require large increases. Regular testing is needed, starting with monthly monitoring in the first trimester to 20 weeks of gestation and at least one TSH measurement between 26 and 32 weeks of gestation.

HYPERTHYROIDISM IN PREGNANCY

Hyperthyroidism is characterised biochemically by a suppressed TSH level and elevated free T_4 and/or T_3 level. It is relatively uncommon, affecting 0.1 to 1.0% of all pregnancies.[1,4]

The most common causes of hyperthyroidism are gestational transient thyrotoxicosis (GTT; or hCG-mediated hyperthyroidism) and Graves' disease (autoimmune hyperstimulation of the thyroid gland by TRAb).[22] These and other less common causes of hyperthyroid states are listed in Box 4. Overt hyperthyroidism (most often Graves' disease) is associated with maternal and fetal adverse outcomes (Box 5).[23] Rare cases of thyroid storm precipitated by infection, pre-eclampsia, caesarean section or parturition have been reported. Subclinical hyperthyroidism is not associated with adverse pregnancy outcomes.[24]

The usual investigations to elucidate the cause of hyperthyroidism involve measurement of TSH, T_4, T_3 and TRAb levels. A nuclear medicine radioiodine uptake scan is sometimes required but is contraindicated during pregnancy.

The goal of therapy is to reduce and maintain the maternal serum free T_4 concentration in the high–normal range using the lowest drug dose. This requires TFTs every four weeks with dose adjustment if needed.[1,2] Table 3 summarises the biochemical features and recommendations in hyperthyroidism.

Gestational transient thyrotoxicosis

Patients may develop elevated free T_4 and/or free T_3 levels in association with a low TSH level, and negative thyroid antibodies in the first trimester. GTT is seen particularly in women with high levels of beta hCG, associated with twin pregnancies and hyperemesis. Thyrotoxic symptoms are difficult to assess in the presence of tachycardia and fatigue, which are common in normal pregnancy.

Patients with hyperemesis and GTT may require hospitalisation for supportive therapy, such as intravenous fluids; low-dose antithyroid drugs are only rarely given for very short periods in overt cases and generally not used in patients with mild GTT. The condition resolves after the first trimester when the beta hCG levels decline. A transient, usually subclinical hyperthyroidism can therefore be considered a normal physiological finding.[4]

Graves' disease

Graves' disease tends to improve during pregnancy due to a reduction in TRAb or, rarely, when the antibodies become blocking in nature rather than stimulatory. A relapse in the condition often occurs in the postpartum period, but there are exceptions to this rule. Patients with Graves' disease are advised not to embark on pregnancy unless their disease is in remission or well controlled with very low doses of antithyroid drugs (or their thyroid has been ablated by surgery or radioactive iodine).

5. ADVERSE OUTCOMES OF OVERT HYPERTHYROIDISM[23]
- Spontaneous abortion
- Premature labour
- Low birthweight
- Stillbirth
- Pre-eclampsia
- Neonatal thyroid disease
- Heart failure

In all patients with Graves' disease regardless of previous therapy the stimulating antibody TRAb can cross the placenta and cause neonatal thyrotoxicosis or hypothyroidism. It is important to measure affected women's TRAb levels through pregnancy to assess fetal risk. About 5% of neonates born to women with Graves' disease have hyperthyroidism due to transplacental transfer of TRAb, and the incidence increases proportionally with the TRAb titre. All women with Graves' disease should therefore be monitored for signs of fetal thyrotoxicosis with measurement of fetal heart rate and assessment of fetal growth with ultrasound.

Patients on very low doses of antithyroid drugs can usually cease their medication in the first trimester if they are TRAb negative. Some patients require ongoing therapy, and in such cases it is best to switch treatment to propylthiouracil in the first trimester, with a dose of carbimazole 5 mg being equivalent to propylthiouracil 50 mg. Studies have suggested a lower rate of congenital malformations in pregnant women taking propylthiouracil versus carbimazole in the first trimester. The guidelines then suggest switching back to carbimazole in the second trimester.[1,2] However, a recent

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2014.

TABLE 3. HYPERTHYROIDISM: ASSOCIATED BIOCHEMISTRY AND TREATMENT RECOMMENDATIONS

Thyroid status and disease	TSH level	T_4 level	TRAb status	Treatment recommended (antithyroid drugs)
Gestational transient thyrotoxicosis	Normal or suppressed	Normal or elevated	Negative	No
Subclinical hyperthyroidism	Suppressed (<0.1) or undetectable (<0.01)	Normal	Negative	No
	Suppressed (<0.1) or undetectable (<0.01)	Normal	Positive	Yes
Overt hyperthyroidism	Suppressed (<0.1) or undetectable (<0.01)	Elevated	Negative	Yes
	Suppressed (<0.1) or undetectable (<0.010)	Elevated	Positive (Graves' disease)	Yes

ABBREVIATIONS: T_4 = thyroxine; TRAb = thyroid receptor antibodies; TSH = thyroid-stimulating hormone.

Danish study reported a similar prevalence of birth defects with both propylthiouracil and carbimazole use.

Carbimazole and propylthiouracil are associated with urinary system malformation, and propylthiouracil with malformations of the face, head and neck. Choanal atresia, oesophageal atresia, omphalocoele, omphalomesenteric duct anomalies and aplastis cutis are reported in children exposed to carbimazole.[25] Carbimazole is otherwise the treatment of choice for patients with Graves' disease managed medically due to its longer duration of action, lower risk of liver toxicity and more pleasant taste. TFTs should be monitored every four to six weeks in woman taking antithyroid drugs.

Thyroidectomy is rarely necessary in pregnancy but if needed should be delayed until the second trimester.

Thyroid function should be tested in the cord blood of the baby on delivery. Graves' disease symptoms will often flare in the mother in the postpartum period. Studies in breastfeeding mothers are small, but it is considered that doses of carbimazole of 20 mg or less are safe; splitting the dose and taking it after breastfeeding is recommended.

THYROXINE REPLACEMENT IN PREGNANCY AND POSTPARTUM

Patients who have undergone total thyroidectomy will require an increase in their thyroxine dose of at least 30% in early pregnancy. They should be advised to increase their dose automatically at the time of conception and have regular TFT testing, at least monthly in the first trimester. A useful initial rule is to instruct the patient to take the equivalent of two extra daily doses per week once pregnancy is confirmed.

Patients with an intact thyroid are usually advised to increase their dose of thyroxine but some will become over-replaced in pregnancy with this strategy so they also require regular TFT monitoring. It is important to remember to tell women to take thyroxine separately to their other vitamins, including iron and calcium supplements, due to the binding that can occur, decreasing the efficacy of absorption.

Endocrinologists are now seeing patients referred for minor aberrations in TSH levels with normal T_4 levels. Some of these patients will have underlying autoimmune hyperthyroid disease (especially if antibodies are positive), whereas others will revert to normal levels after pregnancy and will not require long-term thyroxine treatment. Family history and the presence or absence of antibodies will help to distinguish these two scenarios.

It is recommended that patients return to their pre-pregnancy thyroxine dose in the postpartum period. It is important to reassess patients during this time as most cases of maternal isolated hypothyroxinaemia and subclinical hypothyroidism are transient, so treatment with thyroxine needs to be reviewed and likely ceased postpartum.[10]

CONTROVERSIES IN MANAGING EUTHYROID ANTIBODY POSITIVITY

There is insufficient evidence to recommend routine screening of all pregnant women for thyroid antibodies in the first trimester. Indeed, if patients are euthyroid but thyroid antibody positive, there is insufficient evidence to recommend treatment with thyroxine, even if they are undergoing IVF or have a history of recurrent spontaneous abortion or preterm delivery.

POSTPARTUM THYROID DYSFUNCTION

Patients with ongoing Graves' disease may breastfeed while taking antithyroid drugs; carbimazole in doses of up to 20 to

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2014.

30 mg is safe during lactation. It is best given in divided doses and administered after breastfeeding. Propylthiouracil is second-line therapy and high doses (>300 mg/day) should be avoided due to concerns about hepatotoxicity.

Patients with positive antithyroid antibodies in early pregnancy have about a 30% risk of developing postpartum thyroiditis. This is a self-limiting condition that presents in the first six to 12 months' postpartum. It manifests with transient thyrotoxicosis, transient hypothyroidism or both, and patients often have a full recovery. Some 20 to 40% of patients may develop permanent hypothyroidism and thus monitoring for this is required.[26] Patients who present with postnatal depression must also be assessed for postpartum thyroiditis.

It can sometimes be difficult to distinguish postpartum thyroiditis from Graves' disease; however, patients with Graves' disease will usually present with more marked TFT disturbance, positive TRAb, more pronounced symptoms and other features including larger thyroid size and thyroid eye disease. The two conditions can be distinguished on technetium-99 nuclear uptake scan (low uptake versus diffuse increased uptake) but these scans are usually not needed and are unsuitable for women who are breastfeeding.

During the thyrotoxic phase, symptomatic patients are treated with propranolol. Antithyroid drugs are not used, but thyroxine may be needed in the hypothyroid phase in some patients who are symptomatic. Patients with asymptomatic hypothyroidism may not require treatment but TSH monitoring is important to document recovery and exclude ongoing Hashimoto's disease, especially if they are considering another pregnancy. Similarly, patients treated with thyroxine should try tapering (and ceasing) their therapy after three to six months unless they are planning to conceive again in the near future.

Women with a prior history of postpartum thyroiditis should have ongoing annual TSH level measurement to monitor for the onset of permanent hypothyroidism.

MANAGEMENT OF THYROID NODULES AND THYROID CANCER DURING PREGNANCY

Mild diffuse thyroid swelling is common in normal pregnancy and nodules may be detected clinically or on imaging. Thyroid nodules should be assessed with neck ultrasound and TSH level measurement. If there is concern about the size or behaviour of a nodule or its appearance on ultrasound, they may be biopsied under ultrasound guidance with fine-needle aspiration biopsy [FNAB] in the same way as if the woman were not pregnant.[1,2] Otherwise FNAB can be deferred to the postpartum period. Any patient with atypical or malignant thyroid cytology during pregnancy should be referred to a specialist.

If surgery is deemed to be appropriate during pregnancy, it is usually deferred until the second trimester, where it carries no greater risk to the fetus or woman than it would during the postpartum period. Some patients with small well-differentiated thyroid cancers can have surgery deferred to the postpartum period but they need regular neck ultrasound during pregnancy to monitor the growth of the malignant nodule. More detail is given in both the American and European Thyroid Associations guidelines.[1,3]

Imaging or therapy with radioactive iodine or other isotopes is not advised in pregnancy. Previous therapy with radioactive iodine for thyroid cancer or Graves' disease given at least six months before pregnancy will not adversely affect the outcome of the pregnancy or the fetus.

Patients with thyroid cancer diagnosed during pregnancy will need to be counselled about whether breastfeeding is feasible and for how long, noting that radioactive iodine ablation will have to be postponed for several months after cessation of breastfeeding. These decisions are made on an individual basis, based on the histopathology, staging and risk assessment of the cancer. The patient should be referred to a thyroid unit with multidisciplinary input.

CONCLUSION

It is important to detect significant thyroid dysfunction at the time of conception or as early as possible in the first trimester so that appropriate therapy can be promptly instituted to optimise maternal and fetal outcomes. Appropriate therapy and monitoring of both the mother and fetus during pregnancy and into the postpartum period is guided by the clinical scenario, past and family history, degree of TFT derangement and autoimmune status. Universal screening for thyroid dysfunction in pregnancy during the first trimester with measurement of TSH levels is generally recommended. MT

REFERENCES

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

Online CPD Journal Program

© DEVIANT FT/DOLLAR PHOTO CLUB

The World Health Organization recommends that pregnant women take an iodine supplement of 150 µg/day. True or false?

Review your knowledge of this topic and earn CPD/PDP points by taking part in MedicineToday's Online CPD Journal Program.

Log in to
www.medicinetoday.com.au/cpd

Downloaded for personal use only. No other uses permitted without permission. © MedicineToday 2014.

Recognising and managing thyroid dysfunction in pregnancy

REFERENCES

1. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; 21: 1081-1125.
2. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; 97: 2543-2565.
3. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 2014; 3: 76-94.
4. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev 2010; 31: 702-755.
5. Julvez J, Alvarez-Pedrerol M, Rebagliato M, et al. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology 2013; 24: 150-157.
6. Henrichs J, Bongers-Schokking JJ, Schenk JJ, et al. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab 2010; 95: 4227-4234.
7. Vaidya B, Hubalewska-Dydejczyk A, Laurberg P, Negro R, Vermiglio F, Poppe K. Treatment and screening of hypothyroidism in pregnancy: results of a European survey. Eur J Endocrinol 2012; 166: 49-54.
8. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987; 65: 689-696.
9. Ballabio M, Poshychinda M, Ekins RP. Pregnancy-induced changes in thyroid function: role of human chorionic gonadotropin as putative regulator of maternal thyroid. J Clin Endocrinol Metab 1991; 73: 824-831.
10. Shields BM, Knight BA, Hill AV, Hattersley AT, Vaidya B. Five-year follow-up for women with subclinical hypothyroidism in pregnancy. J Clin Endocrinol Metab 2013; 98: E1941-E1945.
11. Delange F. Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodine nutrition. Public Health Nutr 2007; 10: 1571-1580.
12. National Health and Medical Research Council. Iodine supplementation for pregnant and breastfeeding women. Canberra: NHMRC; 2010. Available online at: http://www.nhmrc.gov.au/guidelines/publications/new45 (accessed December 2014).
13. Charlton KE, Gemming L, Yeatman H, Ma G. Suboptimal iodine status of Australian pregnant women reflects poor knowledge and practices related to iodine nutrition. Nutrition 2010; 26: 963-968.
14. Fitzpatrick DL, Russell MA. Diagnosis and management of thyroid disease in pregnancy. Obstet Gynecol Clin North Am 2010; 37: 173-193.
15. Gilbert RM, Hadlow NC, Walsh JP, et al. Assessment of thyroid function during pregnancy: first-trimester (weeks 9-13) reference intervals derived from Western Australian women. Med J Aust 2008; 189: 250-253.
16. Lee RH, Spencer CA, Mestman JH, et al. Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol 2009; 200: 260. e1-6.
17. Hallengren B, Lantz M, Andreasson B, Grennert L. Pregnant women on thyroxine substitution are often dysregulated in early pregnancy. Thyroid 2009; 19: 391-394.
18. LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? Thyroid 2005; 15: 60-71.
19. Negro R, Stagnaro-Green A. Diagnosis and management of subclinical hypothyroidism in pregnancy. BMJ 2014; 349: g4929.
20. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012; 22: 1200-1235.
21. Vissenberg R, van den Boogaard E, van Wely M, et al. Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. Hum Reprod Update 2012; 18: 360-373.
22. Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract 2011; 17: 456-520.
23. Mannisto T, Vaarasmaki M, Pouta A, et al. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. J Clin Endocrinol Metab 2010; 95: 1084-1094.
24. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol 2006; 107(2 Pt 1): 337-341.
25. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. J Clin Endocrinol Metab 2013; 98: 4373-4381.
26. Stagnaro-Green A. Approach to the patient with postpartum thyroiditis. J Clin Endocrinol Metab 2012; 97: 334-342.

Downloaded for personal use only. No other uses permitted without permission. © **Medicine**Today 2014.