Thyroid dysfunction in pregnancy

Optimising obstetric outcomes

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Thyroid dysfunction is not uncommon in pregnancy. Women at high risk should be screened early and treated to optimise obstetric outcome. Women with pre-existing thyroid dysfunction should have their thyroid function optimised preconception.

About 3% of women have some form of thyroid dysfunction during pregnancy. Assessment of these women requires an understanding of the changes in thyroid physiology during pregnancy. Proper management is important to ensure maternal and fetal wellbeing for an optimal obstetric outcome.

This article describes thyroid physiology in normal pregnancy and the investigation and management of women with hypothyroidism and hyperthyroidism, as well as thyroid nodules and cancer during pregnancy. Recently, excellent evidence-based guidelines have been published.[1,2] However, questions still remain and further clinical research is required to resolve uncertainties.

Thyroid physiology in normal pregnancy

During early pregnancy, high levels of human chorionic gonadotrophin (hCG) stimulate the thyroid-stimulating hormone (TSH) receptor. This results in a 10 to 20% enlargement in the thyroid gland, a 30 to 50% increase in thyroxine (T_4) and triiodothyronine (T_3) production, and a decrease in TSH levels.

Thyroid hormone requirement is higher during pregnancy due to an increase in plasma volume leading to an altered distribution of thyroid hormone, increased thyroid hormone metabolism, increased renal clearance of iodide, and higher levels of hepatic production of thyroxine-binding globulin in the hyperoestrogenic state.[3] This explains the need to increase daily iodine consumption to 250 µg in pregnant and lactating women, as recommended by the World Health Organization.[4]

Serum T_4 and T_3 values reach a plateau at the end of the first trimester. The fetal thyroid does not begin to function until the 12th to 18th week of pregnancy; therefore, adequate maternal T_4 supply is essential in the first trimester for normal fetal neurological development. Following the fall in hCG levels after the first trimester, free T_4 levels decrease and TSH levels increase. Thyroxine-binding globulin remains high until delivery (see Figure).[5]

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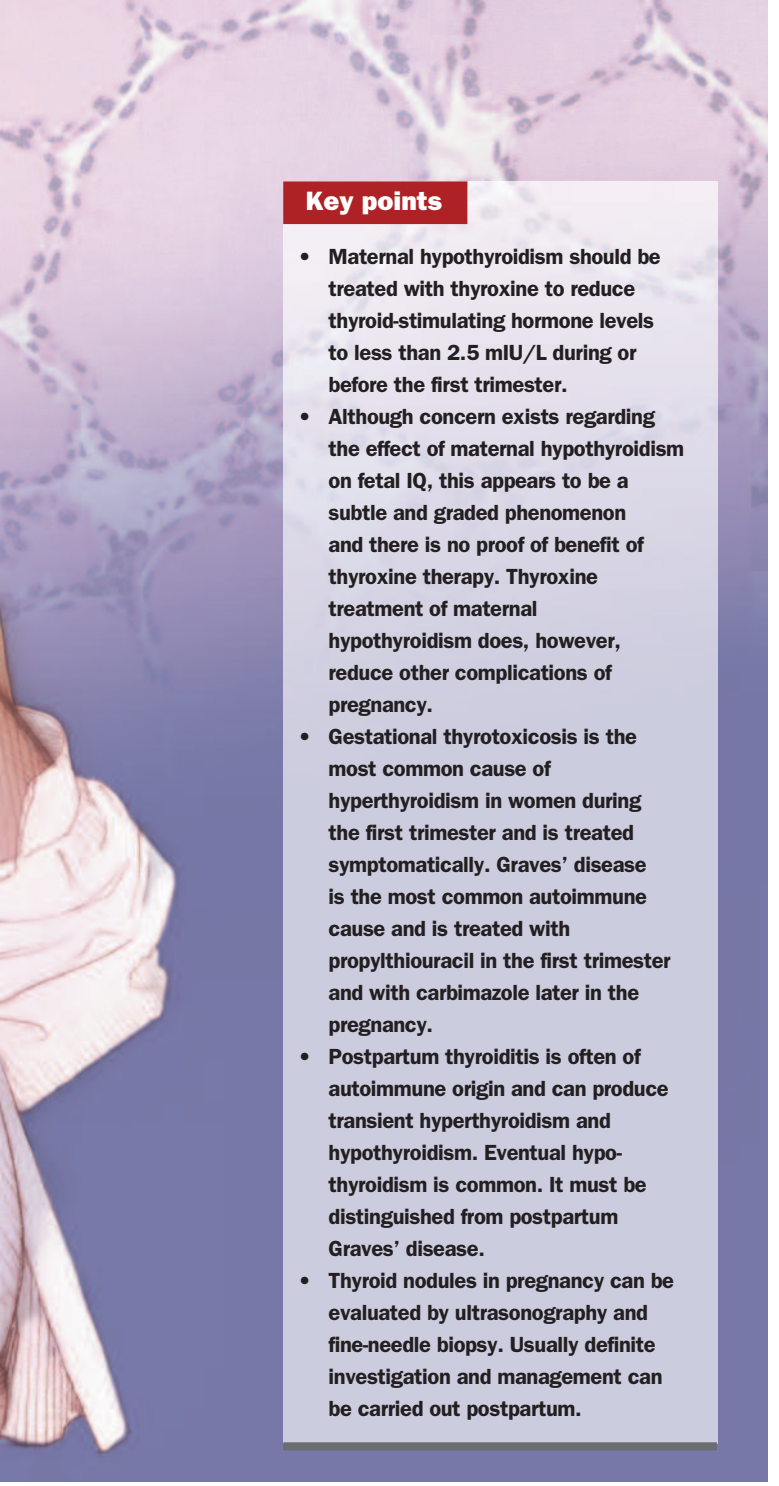


Key points

- **Maternal hypothyroidism should be treated with thyroxine to reduce thyroid-stimulating hormone levels to less than 2.5 mIU/L during or before the first trimester.**
- **Although concern exists regarding the effect of maternal hypothyroidism on fetal IQ, this appears to be a subtle and graded phenomenon and there is no proof of benefit of thyroxine therapy. Thyroxine treatment of maternal hypothyroidism does, however, reduce other complications of pregnancy.**
- **Gestational thyrotoxicosis is the most common cause of hyperthyroidism in women during the first trimester and is treated symptomatically. Graves' disease is the most common autoimmune cause and is treated with propylthiouracil in the first trimester and with carbimazole later in the pregnancy.**
- **Postpartum thyroiditis is often of autoimmune origin and can produce transient hyperthyroidism and hypothyroidism. Eventual hypothyroidism is common. It must be distinguished from postpartum Graves' disease.**
- **Thyroid nodules in pregnancy can be evaluated by ultrasonography and fine-needle biopsy. Usually definite investigation and management can be carried out postpartum.**

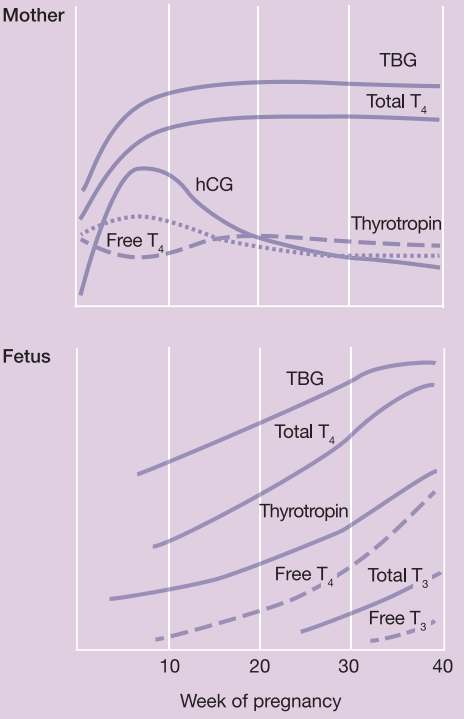


Figure. Relative changes in maternal and fetal thyroid function during pregnancy.

Abbreviations: hCG = human chorionic gonadotrophin; TBG = thyroxine-binding globulin.

Adapted with permission from Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med 1994; 331: 1072-1078.[5]

These dynamic changes indicate that pregnancy-specific and, ideally, trimester-specific reference ranges for thyroid function tests are important in the proper assessment of thyroid status during pregnancy. The American Thyroid Association (ATA) has recommended that if trimester-specific reference ranges for TSH are not available in the laboratory, the following ranges can be used:[1]

- 0.1 to 2.5 mIU/L for the first trimester
- 0.2 to 3.0 mIU/L for the second trimester
- 0.3 to 3.0 mIU/L for the third trimester.

As total T_4 rises during pregnancy to 150% of the nonpregnant range due to increased levels of thyroxine-binding globulin, the nonpregnant total T_4 range can be adapted by multiplying by 1.5.[2] However, in Australia, total T_4 measurement is no longer routinely available and free T_4 estimates are usual, but the interpretation of free T_4 values in pregnancy is problematic. Free T_4 estimates are assay-specific and tend to fall during pregnancy to values below the nonpregnant reference range, particularly in the second and third trimesters. This should not be interpreted as hypothyroidism in the absence of raised TSH levels.

Hypothyroidism

Prevalence and causes

About 2 to 3% of women of a reproductive age have hypothyroidism, of whom 0.3 to 0.5% have overt hypothyroidism and 2.0 to 2.5% have subclinical hypothyroidism.[2]

Apart from severe iodine deficiency (not present in Australia), chronic autoimmune thyroiditis is the main cause of hypothyroidism. Other causes include previous radioactive iodine therapy or thyroid surgery, and (rarely) central hypothyroidism/hypopituitarism.

Complications

Overt hypothyroidism confers an increased risk of maternal complications, such as anaemia, infertility, miscarriage, gestational hypertension, placental abruption and postpartum haemorrhage. It also increases the risk of the adverse fetal outcomes of prematurity, low birth weight, respiratory distress and fetal death (see the box on page 10).

Subclinical hypothyroidism is also associated with an increased risk of complications mentioned above, although the data are more variable compared with overt hypothyroidism. A seven-point intelligence quotient deficit in the offspring of untreated women with subclinical hypothyroidism (mean free T_4 level of 95 nmol/L, mean TSH level of 13.2 mIU/L) has been described, in addition to developmental delays in motor, language and attention at 7 to 9 years of age, demonstrating an adverse effect of maternal hypothyroidism on fetal neurocognitive development.[6] However, a recent trial of thyroxine therapy in women with subclinical hypothyroidism after the 12th week of pregnancy found no neuropsychometric benefit.[7]

Maternal and fetal complications caused by overt hypothyroidism

Maternal complications
Subfertility/infertility
Anaemia
Miscarriages
Gestational hypertension
Placental abruption
Postpartum haemorrhage

Fetal complications
Prematurity
Small for gestational age
Respiratory distress
Impaired neurocognitive development
Death

Profiles of high-risk women for targeted screening of thyroid dysfunction

- Symptoms of thyroid dysfunction (hypothyroidism and hyperthyroidism)
- Goitre or thyroid nodules
- Presence of thyroid autoantibodies
- Type 1 diabetes or other autoimmune conditions
- Previous head or neck irradiation or surgery
- Subfertility or infertility
- Previous poor obstetric outcomes
- Family history of autoimmune thyroid disease
- Residing in areas with iodine deficiency

Screening

As described above, it is important to ensure maternal euthyroidism preconception and during pregnancy. Many obstetricians perform routine thyroid function testing at the initial consultation. However, universal antenatal thyroid screening has not been advocated by the ATA or the US Endocrine Society in their recent guidelines in 2011 and 2012, respectively. The Asia and Oceania Thyroid Association, of which Australia is a part, had representatives in the taskforce for both guidelines.

It is currently recommended that case-finding testing should only be offered to women at high risk of thyroid dysfunction (see the box on this page). Nevertheless, recent studies tend to favour universal screening. Although one study has found that universal screening compared with case finding screening did not reduce adverse outcomes, case finding in high-risk women failed to detect the majority of thyroid dysfunction in pregnancy, and the treatment of thyroid dysfunction in a low-risk group was associated with a lower rate of adverse outcomes.[8] Another study found that in the medical structure of the USA, universal screening is cost effective compared with risk-based screening, and both strategies are cost effective compared with no screening.[9] In our opinion, universal screening will eventually become the standard of care.

Treatment

Women with overt hypothyroidism should be treated promptly and fully with thyroxine replacement to reach a treatment target TSH level of less than 2.5 mIU/L preconception and during the first trimester, and less than 3.0 mIU/L during the second and third trimesters.[2] Thyroid function should be monitored every four weeks during the first half of pregnancy and every six to eight weeks in the second half.

There is controversy over treating subclinical hypothyroidism in pregnancy. The ATA recommends against treatment unless antithyroid peroxidase antibodies (aTPO) are also elevated.[1] These women should be monitored for progression to overt hypothyroidism throughout pregnancy. The US Endocrine Society, however, has recommended thyroxine replacement for all cases of subclinical hypothyroidism, regardless of aTPO status.[2]

Treating euthyroid women with elevated aTPO levels

Up to 20% of pregnant women have elevated aTPO levels, an important marker for the development of hypothyroidism. Although there is suggestion of an association of thyroid autoimmunity (in the absence of a raised TSH level) with pregnancy loss,[10] the data are not conclusive. Hence, women who are euthyroid with elevated aTPO levels do not need to be treated, but require close monitoring of thyroid function during pregnancy.[1,2]

Treating women with pre-existing hypothyroidism

Thyroxine requirement increases during pregnancy from four to six weeks of gestation onwards, through to midgestation and then plateaus until delivery. Hence, women with pre-existing hypothyroidism need to increase their thyroxine dose as soon as pregnancy is confirmed by 30 to 50% (depending on presence/absence of residual functional thyroid tissue).[11,12] A useful guide is to increase the weekly total dose by the equivalent of two daily doses. Thyroid function should be monitored every four weeks during the first half of pregnancy and at least once between the 26th and 32nd week of gestation.[1] Following delivery, thyroxine should be reduced to the preconception dose and thyroid function checked at six weeks postpartum.[1]

Hyperthyroidism

Prevalence and causes

Hyperthyroidism during pregnancy is less common than hypothyroidism, with a prevalence of 0.2%.[13] Apart from gestational thyrotoxicosis, the causes of hyperthyroidism are similar to nonpregnant women and include Graves' disease, toxic adenoma, multinodular

goitre, thyroiditis and, rarely, TSH-producing pituitary adenoma and partial thyroid hormone resistance.

Gestational thyrotoxicosis is defined as transient hyperthyroidism and is limited to the first half of pregnancy. It is characterised by elevated free T_4 levels and suppressed TSH levels, in the absence of serum markers of autoimmunity.[14] It occurs in 1 to 3% of pregnancies and is the most common overall cause of hyperthyroidism during pregnancy.[14] Gestational thyrotoxicosis is secondary to elevated hCG levels. TSH receptors are stimulated by hCG due to its structural homology with TSH. Gestational thyrotoxicosis is associated with hyperemesis gravidarum, defined as severe nausea and vomiting in early pregnancy, with more than a 5% weight loss, dehydration and ketonuria.

Assessment

It is important to distinguish gestational thyrotoxicosis from Graves' disease (the next most common cause in 0.1 to 1% of pregnancies) and other causes because management depends on the aetiology. Assessment includes:

- enquiring about the onset and duration of thyrotoxic symptoms, which may predate pregnancy in Graves' disease
- enquiring about a previous or family history of autoimmune thyroid disease
- performing a clinical examination looking for evidence of Graves' disease, such as diffuse goitre with bruit and Graves' ophthalmopathy
- testing for TSH receptor antibodies (TRAb), which are usually present in patients with Graves' disease.

Complications

Uncontrolled hyperthyroidism in pregnancy can cause pre-eclampsia, congestive cardiac failure, placental abruption and thyroid storm in pregnant women. In addition, the fetus is also at risk of thyroid dysfunction, spontaneous abortion, premature labour, low birth weight and congenital abnormalities (see the box on this page).

Treatment

Treatment of hyperthyroidism in pregnancy depends on its aetiology. It is recommended that the GP consider consultation with an endocrinologist experienced in the assessment and management of hyperthyroidism in pregnancy.

In contrast to subclinical hypothyroidism, treatment for subclinical hyperthyroidism is not indicated because there is no evidence that treatment improves pregnancy outcomes and treatment may adversely affect fetal outcomes.[15] Gestational thyrotoxicosis does not require treatment with antithyroid medications because serum T_4 levels normalise by 14 to 18 weeks of gestation with the decline of hCG levels. However, women with severe hyperemesis gravidarum require hydration and correction of electrolyte abnormalities. Low-dose beta blockers may be needed in women with very symptomatic hyperthyroidism, although their use may cause fetal bradycardia, hypoglycaemia,[16] respiratory distress and low birth weight, and should be ceased well before labour if possible.

Pregnant women with Graves' disease and toxic adenoma or multinodular goitre are treated with thionamides. Both carbimazole and propylthiouracil cross the placenta.[17] Carbimazole has been shown to be associated with aplasia cutis and oesophageal/choanal atresia,[18] prompting a recommendation to use propylthiouracil in pregnancy. However, the US Food and Drug Administration recently issued a warning on the increased risk of hepatotoxicity with propylthiouracil, limiting its use to the first trimester of pregnancy when fetal organogenesis occurs,[19] with changeover to carbimazole in the second trimester. During thionamide therapy, guidelines recommend that thyroid function should be checked every two to six weeks,[1] but usually every four to six weeks is sufficient. Although the risk of hepatotoxicity with propylthiouracil and risk of teratogenicity of carbimazole are both very low, we recommend using propylthiouracil in the first trimester then changing to carbimazole for the remainder of the pregnancy. A dose conversion of 10 mg of propylthiouracil to 1 mg of carbimazole is usually satisfactory. The general aim is to use the lowest possible dose of thionamide to keep free T_4 levels at or just

Maternal and fetal complications caused by hyperthyroidism

Maternal complications

Miscarriages
Pre-eclampsia
Congestive cardiac failure
Placental abruption
Thyroid storm

Fetal complications

Thyroid dysfunction
Prematurity
Small for gestational age
Congenital abnormalities

above the upper limit of normal, to lower the risk of medication-induced embryopathy and to prevent overtreatment leading to fetal hypothyroidism.[20] In women with uncontrolled hyperthyroidism, despite high doses of thionamides, and in those with serious adverse reactions to thionamides, thyroidectomy may have to be considered and is best performed in the second trimester of pregnancy.[1]

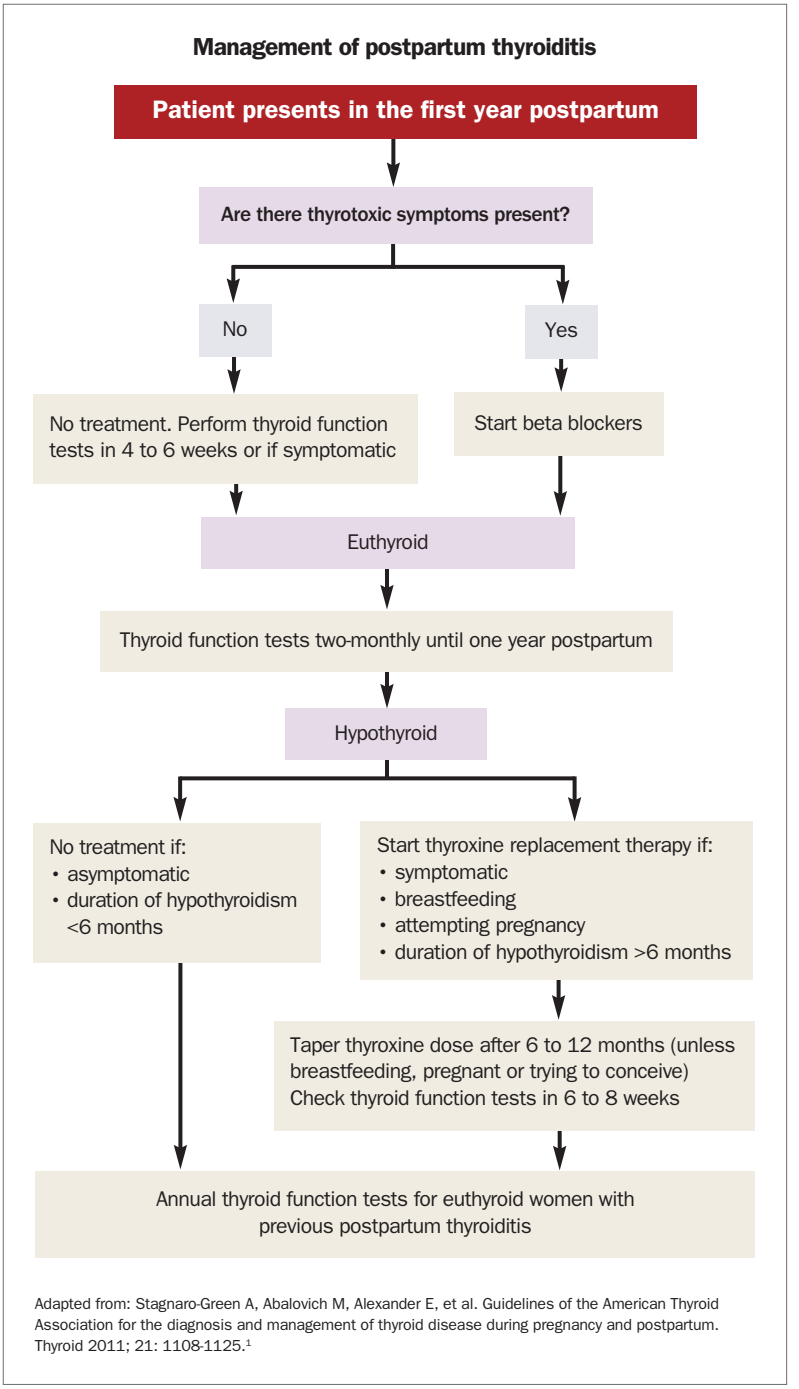
Radioactive iodine is contraindicated during pregnancy. Mistaken administration of radioactive iodine in pregnancy should be avoided by mandatory pregnancy testing before any dose is given. No reports of fetal birth defects have been made with low-dose therapy before 10 weeks of gestation, but fetal thyroid ablation may occur with later dosing, especially with doses of more than 15 mCi (550 MBq).[21]

Treating women with pre-existing Graves' disease

Women with Graves' disease should be advised to conceive only after the euthyroid state has been achieved while taking no or low-dose medication. After radioactive iodine therapy, at least four months should lapse before conception,[22] but a minimum of six months before conception is often recommended.

The natural course of Graves' disease in pregnancy is an exacerbation in the first trimester, followed by gradual improvement in the second and third trimesters. In 20 to 30% of women, cessation of antithyroid medications in the last trimester is required.[23] Hence, close monitoring of thyroid function throughout pregnancy is important.

TRAb are present not only in women with active Graves' disease, but may also be present in those who have received ablative therapy (radioactive iodine or surgery) previously. Transplacental passage of maternal TRAb can lead to fetal hyperthyroidism. The greatest risk of neonatal hyperthyroidism is with markedly elevated stimulatory TRAb.[24] Hence, maternal determination of TRAb should be obtained at the 20th to 24th week of gestation in women with past or present history of Graves' disease.[1] If the level is high (greater than three times the upper limit of normal),[1] or in cases of uncontrolled hyperthyroidism, the fetus should be monitored for ultrasonographic features of hyperthyroidism, such as goitre, tachycardia, intrauterine growth retardation, accelerated bone maturation, congestive cardiac failure and hydrops.[25] Treatment, generally by maternal administration of thionamide, will be needed if the fetus does have hyperthyroidism. Generally fetal/neonatal hyperthyroidism is transient, with clearance of maternal TRAb by three to six months of life,[26] but administration of thionamide to the neonate may be transiently required.



Adapted from: 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: 1108-1125.[1]

It is not uncommon for women with Graves' disease to relapse postpartum due to rebound from the previous immunosuppressed state in pregnancy.[13] Hence, it is important to check thyroid function four to six weeks following delivery.

Both carbimazole and propylthiouracil are excreted in breast milk but only in small amounts; hence, breastfeeding is safe for women as long as the daily doses of these drugs are below 30 mg and 300 mg, respectively.[1] The drug should be taken following breastfeeding, in

divided doses. Radioactive iodine therapy is contraindicated during lactation because it is concentrated in active breast tissue and may have an adverse effect.

Postpartum thyroiditis

Definition and prevalence

Postpartum thyroiditis is defined as the occurrence of autoimmune thyroid dysfunction in the first postpartum year in women who are previously euthyroid.[27] It has a prevalence rate of about 8%,[1] and is significantly more common in women with other autoimmune conditions (e.g. a prevalence of 25% in women with type 1 diabetes mellitus).[28] Women with positive aTPO have a 40 to 60% risk of developing postpartum thyroiditis.[29]

Presentation and clinical course

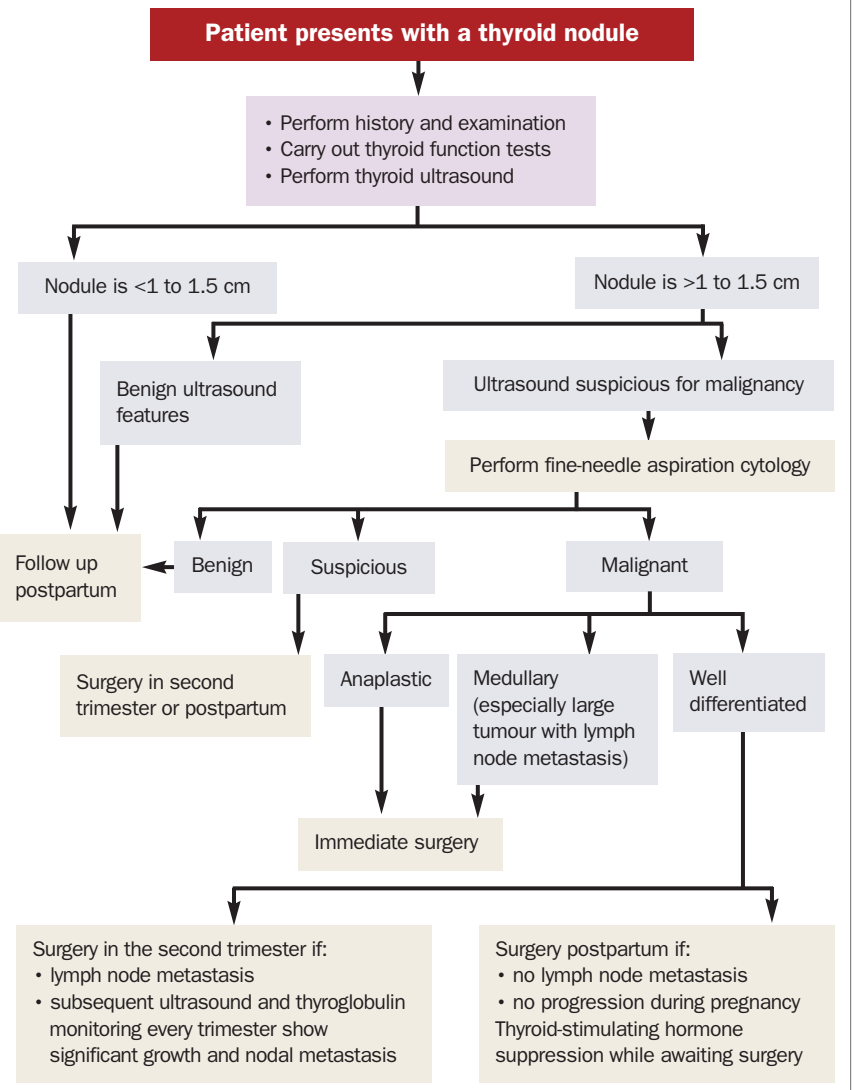
In its classic form, transient hyperthyroidism (which usually occurs two to six months postpartum) is followed by transient hypothyroidism with a return to the euthyroid state by the end of the postpartum year. However, only 25% present in this form, and the rest have either transient isolated hypothyroidism or isolated hyperthyroidism.[29]

Management and follow up

Hyperthyroidism in women with postpartum thyroiditis should be differentiated from relapsed or *de novo* Graves' disease based on history, clinical examination and TRAb testing because the management differs. Postpartum thyroiditis is always transient and does not require treatment with thionamide, although symptomatic women may need to take beta blockers for a few months.

Following resolution of hyperthyroidism, thyroid function should be checked every eight weeks until one year postpartum to screen for hypothyroidism.[1] The hypothyroid phase of postpartum thyroiditis, on the other hand, may result in permanent hypothyroidism in 10 to 20% of cases. Affected women should be commenced on thyroxine replacement, especially if they are symptomatic, breastfeeding or attempting pregnancy. Thyroxine can be tapered after six to 12 months (unless the patient is pregnant, attempting to conceive or breastfeeding) and thyroid function should be checked every six to eight weeks.[1] Women who are euthyroid with a history of postpartum thyroiditis should undergo annual thyroid function tests to evaluate for permanent hypothyroidism (see the flowchart on page 13).[1]

Management of thyroid nodules in pregnancy



Adapted from: 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: 1104-1125.[1]

Thyroid nodules and cancer

Assessment of thyroid nodules

As in the general population, thyroid nodules are common in pregnant women. Most nodules are benign. Risk of malignancy should be stratified by assessing rapidity of nodule growth and compressive symptoms, and taking a history of head and neck radiation and family history of thyroid malignancy. In addition, thyroid function tests should be performed.

If the woman is hyperthyroid, it is most likely that she has a toxic adenoma (especially in the absence of TRAb). Radionuclide scanning and radioactive iodine therapy are contraindicated in

pregnancy and thus empirical thionamide therapy should be used. Thyroid function tests are usually normal in patients with thyroid cancer. Hence, euthyroid (and hypothyroid) women with thyroid nodules should have an ultrasonographic examination.

Features suggestive of malignancy include: irregular margins, hypoechogenicity, microcalcifications, central vascularity, and suspicious cervical lymphadenopathy. Women with solid nodules larger than 1 cm and with suspicious ultrasound features will need fine needle aspiration cytology (see the flowchart on page 14).[1]

Management

Managing women with differentiated thyroid cancer

Prognosis of differentiated thyroid cancer is not worse in pregnancy, and surgery can usually be postponed until after delivery. Occasionally, early surgery may be indicated in the presence of a large tumour, rapid growth or extensive lymph node metastases, and is best performed in the second trimester.

Pregnant women with confirmed differentiated thyroid cancer require thyroid hormone suppression therapy to keep TSH levels in the low-normal range of 0.1 to 1.5 mIU/L,[1] while awaiting surgery postpartum. They should be monitored for tumour growth by neck ultrasound at each trimester. Ablative therapy with radioactive iodine, if indicated postoperatively, should be given at least four weeks after breastfeeding has ceased and further pregnancy should generally be delayed for at least six months. Breast uptake of radioactive iodine should first be excluded by use of ^{99m}Tc pertechnetate scanning.

Managing women with pre-existing differentiated thyroid cancer

For women with known differentiated thyroid cancer, the target TSH level for thyroid hormone suppression therapy should be individualised according to their risk profile and disease state, as described in the ATA guidelines.[1]

Managing women with medullary and anaplastic thyroid cancer

The impact of pregnancy on women with medullary and anaplastic thyroid cancer is unknown. Women with anaplastic thyroid cancer should undergo immediate surgery due to its aggressive nature.[1] Surgery is also recommended for women with medullary thyroid cancer if it is large or if there are extensive lymph node metastases.[1]

Summary

Thyroid dysfunction is not uncommon, especially in women of reproductive age. High-risk individuals should be screened early and treated to optimise obstetric outcome. Women with pre-existing thyroid dysfunction should also have their thyroid function optimised preconception.

The treatment target in pregnant women with hypothyroidism is a TSH level of less than 2.5 mIU/L during the first trimester, and less than 3.0 mIU/L during the second and third trimesters. For those with hyperthyroidism, the target is to use the lowest dose of thionamide to keep free T_4 at or just above the upper normal range. Euthyroid pregnant women with thyroid nodules should have ultrasound examination, and fine-needle aspiration cytology of lesions with suspicious features. Most cases of differentiated thyroid cancer can be surgically treated postpartum by TSH suppression, with thyroxine therapy beforehand. **ET**

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COMPETING INTERESTS: None.